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Dissolution properties and characterization of halofantrine-2-hydroxypropyl-β-cyclodextrin binary systems

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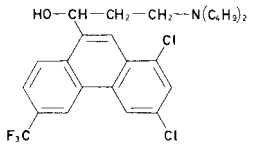
Halofantrine (HF) is a poorly water-soluble antimalarial drug with low bioavailability. Complex formation of HF · HCl and 2-hydroxypropyl-beta-cyclodextrin (HP-β-CD) in aqueous solution and in solid state as well as the possibility of improving the solubility and dissolution rate of the drug though complexation with the cyclodextrin were investigated. Phase-solubility profile indicated that the solubility of the drug was significantly increased in the presence of HP-β-CD and was classified as A_L-type, indicating 1 : 1 stoichiometric inclusion complexes and an apparent stability constant value of 2300 M^{-1}. Solid inclusion complexes of HF · HCl and the cyclodextrin at 1 : 1 molar ratios were prepared by physical mixture, kneading, co-evaporation and freeze-drying methods and characterized by X-ray diffraction and Infra-red spectroscopy. The solubility and dissolution rates of HF · HCl from the complexes were determined and found to be dependent on the preparation method of the complexes. Dissolution profile of the drug was markedly enhanced by complex formation with the cyclodextrin and the product prepared by the freeze-drying method exhibited the most superior dissolution properties compared to the other methods used in this study. The results suggest that the complexation of HF · HCl with HP-β-CD could improve therapeutic efficacy of the drug though enhanced absorption expected from increased drug dissolution.

1. Introduction

Halofantrine (HF) is a phenanthrene-methanol derivative used in the oral treatment of uncomplicated chloroquine- and multidrug-resistant *Plasmodium falciparum* malaria (Bryson and Goa 1992; Karbwang and Bangchang 1994). HF is currently commercially available in the hydrochloride salt as tablets, suspension and capsule. The drug is poorly water soluble and its bioavailability which is low and highly variable (Karbwang and Bangchang 1994) is reported to be about 4.7% (Ajayi 1994). Clinical evaluations of the drug following a standard therapeutic oral regimen (500 mg at 6-hour interval for 3 doses) indicate that majority of observed treatment failures are due to sub-therapeutic plasma levels resulting from poor absorption, rather than drug resistance (Karbwang et al. 1991; Karbwang and Bangchang 1994). The erratic absorption rate of HF also potentially stimulates development of resistance (Charman 1997). Treatment failures with HF have prompted investigations of other dosing regimens or development of different formulations of the drug with a view to improving the oral bioavailability and thus enhancing its clinical success rate (Bouchaud et al. 1994; Oht et al. 1995; Khoo et al. 2000; Abdul-Fattah and Bhargava 2002). The low absorption rate of HF is enhanced when the drug is taken with fatty food (Milton et al. 1989) but the drug is recommended to be administered at a distance from meals. This is because concentration-dependent cardiotoxic effects can result from high plasma levels of the drug that follow food ingestion, and furthermore, ethnic differences in fatty food intake constitute a source of variability.



Halofantrine

Oral bioavailability of poorly water soluble drugs has been improved by several techniques which are designed to increase the aqueous solubility of the drugs. Modification of drug crystal forms, addition of co-solvents, addition of surfactants, and addition of cyclodextrins (CD) are some of such techniques. No attempt has been made to enhance the dissolution properties of HF by formulation of binary systems with cyclodextrins. Cyclodextrins are cyclic (α-1,4)-linked oligosaccharides containing a relatively hydrophobic central cavity and hydrophilic outer surface. Cyclodextrins and their derivatives have aroused considerable interest in the pharmaceutical field because of their potential to form inclusion complexes both in

solution and in solid state with a wide variety of drug molecules (Loftson and Brewster 1996). This can lead to alteration of the physical, chemical and biological properties of the guest molecule which is surrounded by the hydrophobic environment of the cyclodextrin cavity (Loftson and Brewster 1996; Connors 1997; Stella and Rajiwski 1997). Out of the thee parent cyclodextrins, beta-cyclodextrin appears most useful as a pharmaceutical complexing agent because of its complexing ability, low cost and other properties. There is copious literature on the advantages of complexation of drugs with cyclodextrins and these include increased solubility; enhanced bioavailability; improved stability; the masking of bad taste or odour; reduced side effects; and the possibility of a drug release system.

Since the poor aqueous solubility of HF limits its therapeutic effectiveness due to the resultant low and erratic bioavailability, it was thought worthwhile to investigate the possibility of enhancing the solubility and dissolution rate of the drug by forming inclusion complex with 2-hydroxypropyl-β-cyclodextrin (HP-β-CD). The complexes of HF · HCl with HP-β-CD were prepared by different methods and physicochemical determinations based on powder x-ray diffractometry (PXRD) and IR spectroscopy were used to characterize the complexes.

2. Investigations, results and discussion

2.1. Phase-solubility studies

The phase-solubility technique permits evaluation of the affinity between the drug and the cyclodextrin in water. It is useful for investigation of inclusion complexation with cyclodextrins in water because it gives not only the solubilizing ability of the CD, but also provides the stability constant through the analysis of the curve. The phase solubility diagram of the complex formation between HF · HCl and HP-β-CD is shown in Fig. 1. The aqueous solubility of the drug increased linearly with a slope of 0.0225 ($r^2 = 0.993$), as a function of HP-β-CD concentration. The phase solubility diagram can be classified as type A_L according to Higuchi and Connors (1965) and indicates that a soluble complex was formed. Since the slope of the diagram was less than 1, the stoichiometry of the complex was assumed to be 1 : 1. The apparent stability constant (Kc), calculated from the equation (Eq. 1) described in the methods was found to be 2300 M^{-1}. This value of Kc is within the range of 200–5000 M^{-1} considered adequate for the formation of an inclusion complex which may contribute to improving the bioavailability of poorly water soluble drugs like HF (Yamada et al. 2003). The results of the present study are in conformity with earlier reports of investigation of the solubilities of poorly water soluble antimalarial drugs: artemisinin, artemether, dihydroartemisinin, and 10-deoxoartemisinin in 2-hydroxypropyl-β-cyclodextrin solutions. The phase-solubility profiles of these drugs in the cyclodextrin solutions, in the concentration range studied, were classified as type A_L or soluble 1 : 1 complexes (Illapakurthy et al. 2003). Following the addition of HF · HCl to the various aqueous concentrations of the cyclodextrin, the pH of the media (pH 5.70–5.80) were comparable to that of distilled water containing the drug. Therefore, pH played no role in increased solubility of the drug observed in aqueous HP-β-CD solutions.

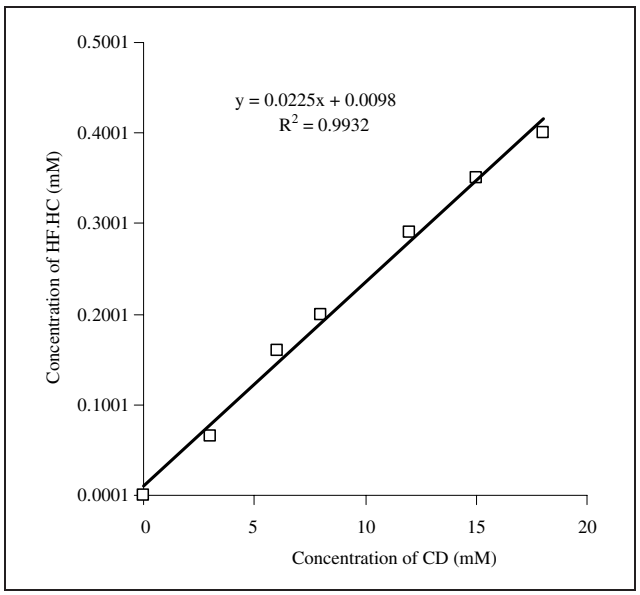


Fig. 1: Phase solubility diagram of halofantrine HCl in aqueous 2-hydroxypropyl-β-cyclodextrin solution. The experimental conditions were as described in the text

2.2. Infrared spectroscopy

The IR spectrum of HF · HCl showed a broad band with a peak at 3267 cm^{-1} and this is indicative of a stretching vibration of the secondary hydroxyl (OH) group with some possible intramolecular interaction between lone pair of electrons on the tertiary nitrogen and the OH group. The intramolecular H-bonding shifts the band to a lower wave number as observed. The presence of this band provides a strong diagnostic point for detection of interactions between the drug and other molecules due to possibility of intermolecular H-bonding. The peaks at 2954 and 2869 cm^{-1} of the spectrum of HF · HCl represent asymmetric CH_3 and CH_2 stretching vibrations. These bands are not of high value in evaluating intermolecular hydrogen bonding and hence not diagnostic of interaction between HF and other molecules. The spectrum also displayed absorption bands at 1659, 1585 and 1465 cm^{-1}, representing the presence of aromatic ring. The IR spectrum of HP-β-CD showed prominent absorption bands at 3417 cm^{-1} (for OH stretching vibrations), 2916 cm^{-1} (for C-H stretching vibrations), and bands in the range of 1355–1470 representing CH_2 and CH_3 bending vibrations. Different degrees of changes are apparent in the IR spectra of the binary systems compared to those of the pure drug and cyclodextrin. There was a shifting of the O–H stretching vibration of cyclodextrin from 3417 cm^{-1} to 3372, 3393, 3378 and 3394 cm^{-1} in the IR spectra of the binary systems prepared by physical mixture (PM), kneading, co-evaporation or freeze-drying methods, respectively. These suggest weak H-bonding interactions between the drug and the hydroxyl groups of the cyclodextrin. A broad peak at 2127 cm^{-1}, corresponding to C–CH (terminal) stretching vibrations in the IR spectrum of cyclodextrin, was retained in the PM, slightly suppressed in the kneaded system (KS) and co-evaporated system (CS) but totally suppressed in the spectrum of freeze-dried system (FS). This is suggestive of non-H-bonding (hydrophobic) interactions occurring in varying degrees in the binary systems, with the highest degree of interaction produced by the freeze-drying method. Furthermore, there were qualitative differences in the finger print regions of the IR spectra of the pure com-

pounds (HF and cyclodextrin) compared to those of the various binary systems. The intensities of the bands in this region (finger print) of the binary systems were reduced to varying extents along with slight shifts in the peaks relative to those of the pure compounds. Suppression of these bands was most evident with freeze-dried systems. These provide further evidence of interaction between the two compounds.

2.3. X-ray diffractometry studies

Powder x-ray diffractometry (PXRD) is a useful method for the detection of cyclodextrin complexation in powder or microcrystalline states. If a true inclusion complex is formed, the diffraction pattern of the complex would be clearly distinct from the superposition of each of the components of the system. Quantitatively, the extent of complex formation can be assessed by calculation of relative degree of crystallinity (RDC). [$RDC = I_{sam}/I_{ref}$ where I_{sam} is peak height of the sample under investigation and I_{ref} is the peak height of the same angle for the reference with the highest intensity (Ryan 1986)]. The PXRD patterns of HF · HCl, the cyclodextrin, and prepared binary systems are presented in Fig. 2A to 2F. The pattern of the pure drug showed peaks that were intense and sharp (Fig. 2A), thus, indicating a crystalline nature of the compound. However, the PXRD pattern of cyclodextrin had a single broad peak and many undefined, diffused peaks with low intensities and this is in agreement with diffractograms earlier reported for the compound (Baboota et al. 2005). This is a reflection of the amorphous nature of cyclodextrins. Some of the principal peaks of HF · HCl and the cyclodextrin were present in the diffraction patterns of PM and KS although with slightly lower intensities. The CS and FS had fewer sharp peaks of much reduced intensities in their diffractograms compared with that of HF · HCl. These indicate that the crystalline nature of HF · HCl is reduced to varying degrees in the binary systems due to partial or complete inclusion complex formation.

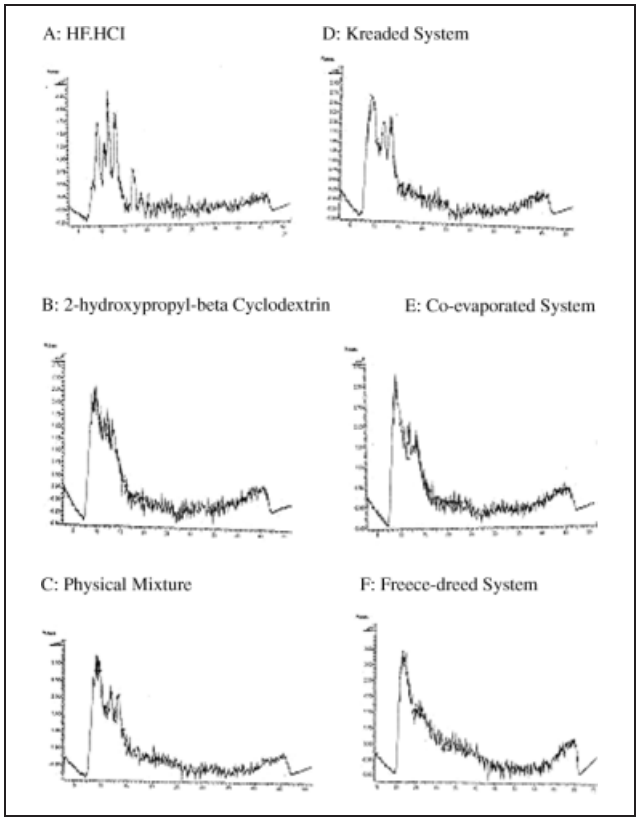


Fig. 2: Powder X-ray diffractograms of halofantrine HCl, 2-hydroxypropyl-β-cyclodextrin, and their binary systems.

The pure drug peak at 11.69° 2θ was used for calculating the RDC and the values for the various binary systems were 0.771, 0.875, 0.917 and 0.979 for the FS, CS, KS and PM, respectively. Since RDC is a measure of extent of complex formation, these results clearly show that the freeze-drying method produced the most efficient inclusion complexation of the drug while the physical mixture method was the least effective.

2.4. Aqueous solubility studies

The aqueous solubilities of HF · HCl and its binary systems with HP-β-CD in simulated gastric fluid (SGF) (without enzyme), pH 1.2, and phosphate buffer, pH 7.4, are shown in Table 1. For all the products, the aqueous solubility was comparatively lower in pH 7.4 than in pH 1.2. This was expected since the drug is weakly basic (pKa 8.2), hence, its ionization increases in acidic media resulting in improved dissolution of the drug. Complexation of HF · HCl with HP-β-CD had a profound effect on increasing the drug solubility and, the method of preparation was also of high significance. All the binary systems yielded significantly higher ($p < 0.05$) solubility of the drug than the pure drug. The enhancement of solubility followed the order of: FS > CS > KS > PM > pure drug in both pH 1.2 and pH 7.4 media. The results indicate that preparation of the binary system by the freeze-drying method can increase the aqueous solubility of HF · HCl by as much as 14-fold in the acidic gastric fluid environment of the stomach. The enhancement of HF · HCl solubility by the various binary systems followed the trend observed in the relative degree of crystallinity of the drug obtained from the X-ray diffractometry studies. This further signifies that the freeze-drying method produced the most superior and efficient inclusion complexation with cyclodextrin. This pattern of improvement of solubility of HF · HCl by the various binary systems as observed in this study have been reported for other highly hydrophobic drugs including celecoxib and furosemide (Vlachou and Papaioannou 2003; Reddy et al. 2004). However, the magnitude of solubility enhancement and the stability constant of formed complexes are specific for each drug. It has been suggested that the effect of complexation with cyclodextrin on the solubility of drugs can be explained in terms of the reduction in the crystallinity of the drug caused by the preparation process and the inclusion of the drug into the hydrophobic cavity of the cyclodextrin (Uekama and Hirayama 1996; Szejtli 1994).

Table 1: Aqueous solubility of halofantrine. HCl and its binary systems with 2-hydroxypropyl β-cyclodextrin at 37 °C

Compound	Aqueous solubility (μg/ml) (Mean ± SD) n = 3	
	pH 1.2	pH 7.4
Pure HF · HCl	0.24 ± 0.01	0.10 ± 0.003
Physical mixture	1.74 ± 0.04	0.22 ± 0.01
Kneaded system	2.10 ± 0.06	0.56 ± 0.02
Co-evaporated system	2.87 ± 0.09	0.63 ± 0.03
Freeze-dried system	3.40 ± 0.10	0.77 ± 0.06

2.5. *In vitro dissolution rate studies*

The dissolution characteristics of the pure drug and binary systems were assessed using percent of active ingredient dissolved at 60 min [$DP_{(60)}$] and 180 min [$DP_{(180)}$] in the dissolution medium. These results are presented in Table 2 and the dissolution profiles are shown in Fig. 3. One-way analysis of variance was used to test the statistical significance of differences between pure drug and binary systems. Significance of difference in the means were tested using Fishers LSD at 95% confidence. The dissolution characteristics of the products in aqueous medium of pH 1.2 were studied to gain information about the dissolution of the drug under the acidic conditions of the stomach. There was a significant difference ($p < 0.05$) between the dissolution rates of the pure drug and any of the binary systems. Also, the dissolution profiles of any pair of the treated samples were markedly different. Overall, the rank order of dissolution rates of the products was: FS > CS > KS > PM > pure drug (Table 2). Thus, the extent of the enhancement of the dissolution rate was found to be dependent on the preparation method, as the freeze-dried, co-evaporated, kneaded and physical mixture products exhibited dissolution rates that were about 24, 8.4, 4.6, and 2 times higher, respectively, than that of the pure drug. The improvement in the dissolution rate, just as in the solubility, of the drug/cyclodextrin systems may result from increased wettability and solubility of the active ingredient by the cyclodextrin as well as the formation of an inclusion complex in the solid state and reduction of the drug crystallinity (Uekama and Hirayama 1996; Trapani et al. 2000; Nallury et al. 2003). In other investigations in which solid cyclodextrin complexes prepared by different methods as used in this study were characterized using additional physicochemical techniques such as differential scanning calorimetry (DSC), proton-nuclear magnetic resonance (^{1}H NMR) spectroscopy and scanning electron microscopy, freeze-dried samples showed the highest dissolution rate than the other preparations and were also conclusively demonstrated to be inclusion complexes (Pose-Vilarnovo et al. 2001; Fernandes et al. 2002; Vlachou and Papaioannou 2003; Reddy et al. 2004; Manca et al. 2005). Thus, although DSC and NMR were not used for physicochemical characterization of the solid complexes prepared in this study, it is reasonable to infer that the freeze-drying method was associated with the most efficient inclusion complex formation, based on the results from the studies of x-ray diffraction and infrared spectroscopy in addition to literature reports. In this study, for the physical and kneaded mixtures, dissolution enhancement is more likely mainly due to the wetting effect of the cyclodextrin and this effect is more apparent for the kneaded system, where the mixing process between the two components was more rigorous. In addition, since cyclodextrins dissolve more rapidly than the pure drug, there is the possibility of an *in situ* inclusion process in the early stages of the dissolution course, and this produces an increase in the amount of the dissolved drug (Corringan and Stanley 1982).

Table 2: Mean ± SD values of percent of active ingredient dissolved for halofantrine HCl and its binary systems with 2-hydroxypropyl β-cyclodextrin at 60 ($DP_{(60)}$) and 180 ($DP_{(180)}$) minutes

Compound	Extent of drug dissolution (%) (Mean ± SD) n = 3	
	$DP_{(60)}$	$DP_{(180)}$
Pure HF · HCl	0.30 ± 0.04	0.52 ± 0.05
Physical mixture	0.58 ± 0.06	0.96 ± 0.06
Kneaded system	1.40 ± 0.10	2.40 ± 0.15
Co-evaporated system	2.52 ± 0.22	4.36 ± 0.24
Freeze-dried System	4.67 ± 0.36	12.65 ± 1.05

The pH and temperature of the dissolution medium were 1.2 and 37 ± 0.5 °C, respectively

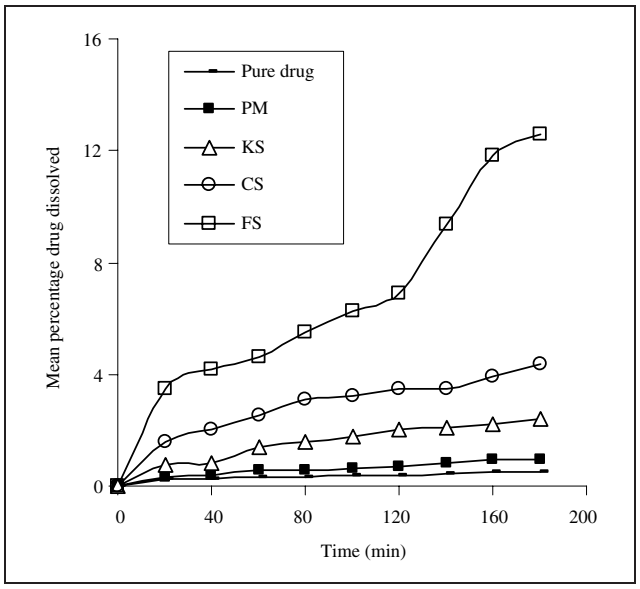


Fig. 3: Dissolution profiles of halofantrine HCl and binary systems with 2-hydroxypropyl-β-cyclodextrin in simulated gastric fluid, pH 1.2 at 37 ± 0.5 °C

In conclusion, the HF · HCl and 2-hydroxypropyl-β-cyclodextrin binary systems prepared by freeze-drying method showed most superior dissolution properties when compared to the co-evaporated system, kneaded system and physical mixture. The results suggest that the complexation of HF · HCl with 2-hydroxypropyl-β-cyclodextrin has the potential to improve therapeutic efficacy of the drug though enhanced dissolution and subsequent increased absorption.

3. Experimental

3.1. *Chemicals and reagents*

Halofantrine HCl (molecular wt 536.42, m.p. 200 °C) was a generous gift from Smithkline Beecham Pharmaceuticals, UK and 2-hydropropyl–β-cyclodextrin (HP-β-CD) was purchased from Sigma-Aldrich Chemical Company (Japan). All reagents used were of analytical grade.

3.2. *Phase-solubility study*

Phase-solubility studies were performed according to the method reported by Higuchi and Connors (1965). HF · HCl, in amounts that exceeded its solubility (30 mg), was taken into glass tubes to which were added 10 mL of distilled water containing various concentrations of HP-β-CD (3–18 mM). The pH of each medium was monitored. These tubes were screw-capped and shaken for 48 h at 25 °C on a rotary flask shaker. Thereafter, as shaking continued, 1.0-ml aliquots were withdrawn at intervals of 12 h and filtered immediately using a 0.45-μm nylon disc filter. The filtered samples were diluted suitably and assayed for HF · HCl by an UV spectrophotometer at 254 nm against blanks prepared in the same concentration of the cyclodextrin in water, so as to exclude any absorbance that may be exhibited by the HP-β-CD. The shaking continued until 3 consutive estimations were the same (96 h). The solubility experiments were conducted in triplicate. The apparent stability constant (K_c) according to the hypothesis of 1 : 1 stoichiometric ratio of complexes was calculated from the phase-solubility diagram using the following equation:

$$K_c = \frac{\text{slope}}{\text{intercept}\,(1 - \text{slope})} \quad (1)$$

The slope was obtained from the straight-line of the plot of HF · HCl concentration against HP-β-CD concentration.

3.3. Preparation of solid binary systems

The binary systems of HF · HCl and HP-β-CD were prepared at 1 : 1 molar ratios using the following methods:

3.3.1. Physical mixture

HF · HCl and HP-β-CD were pulverized, sieved (106 μm) and weighed. The physical mixtures in 1 : 1 molar ratio were prepared by homogenous blending of the powders in a mortar.

3.3.2. Kneading method

The physical mixtures of HF and HP-β-CD in 1 : 1 molar ratios were prepared as described earlier. The binary mixtures were triturated in a mortar with a small volume of water-methanol (1 : 1 vol/vol) solution to obtain a homogeneous paste. The thick slurry was kneaded for 1 h and during this process; an appropriate quantity of water-methanol was added to maintain a suitable consistency. The paste was dried in oven at 40 °C for 24 h. The dried complex was pulverized into a fine powder and sieved (106 μm).

3.3.3. Co-evaporation method

The weights of HF · HCl and HP- β-CD in 1 : 1 molar ratios were used. An aqueous solution of HP-β-CD was added to an alcoholic solution of HF · HCl. The resulting solution was stirred for 1 h and evaporated under vacuum at a temperature of 45 °C in a rotary evaporator. The solid residue was further dried completely at 40 °C for 24 h. The dried complex was pulverized into a fine powder and sieved (106 μm).

3.3.4. Freeze-drying method

The aqueous solution of HP-β-CD and alcoholic solution of HF · HCl containing the required 1 : 1 stoichiometric quantities of the compounds were mixed and agitated with magnetic stirrer for 24 h. The resulting solution was kept in a freezer at −20 °C and lyophilized in a freeze-dryer (Pump deluxe series, DD 150) for 24 h.

3.4. Characterization of solid complexes

The complexes were characterized and evaluated by the following methods:

3.4.1. Infrared (IR) spectroscopy

IR spectra were obtained by an IR spectrophotometer (Buick scientific M_{500} spec) using the KBr disk method (2 mg of sample in 200 mg KBr). The IR scanning range was 4000–500 cm^{-1} and the spectra for each of the binary systems prepared by different methods as well as for pure drug and HP-β-CD were generated.

3.4.2. Powder X-ray diffraction (PXRD) analysis

The PXRD patterns of the pure compounds and the binary systems were recorded using an X-ray diffractometer 25 KV MD10 from Rasicon Ltd (Saint-Petersburg, Russia). Each sample was pulverized into fine powdery form and loaded into the sample holder and irradiated with monochomatized Cu Ka radiation and analysed between 2θ angles of 3 and 70°. The sample exposure time was 1200 s.

3.5. Solubility measurements of HF · HCl and binary systems

The aqueous solubility of the pure drug powder and different binary systems was determined by adding an excess amount of the product, corresponding to 30 mg of HF · HCl, to 10 ml simulated gastric fluid pH 1.2 [containing 2.0 g/L NaCl and 0.065 M HCl in water (USP National Formulary)] or phosphate buffer pH 7.4 [containing 2.38 g/L disodium hydrogen orthophosphate and 0.19 g/L potassium dihydrogen orthophosphate in water (British Pharmacopoeia (1988))] contained in glass tubes. The glass tubes were screw-capped, immersed for 72 h in a thermostat-controlled water bath at 37 ± 0.5 °C 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 though 0.45 μm membrane filters, appropriately diluted and analysed for HF · HCl by UV spectrophotometry. At least triplicate determinations were performed on each sample.

3.6. In vitro dissolution rate studies

The dissolution behaviors of the HF · HCl-HP-β-CD binary systems were compared with those of the pure drug powder. The dissolution rate studies were performed according to the *United States Pharmacopoeia (USP)* XXII rotating basket method at 37 ± 0.5 °C and stirring speed of 100 rpm. The samples, corresponding to 50 mg of HF · HCl, were encapsulated in empty colourless soft gelatin capsules and placed into the rotating basket in the dissolution medium. The dissolution medium was 900 mL of simulated gastric fluid (SGF) pH 1.2 without pepsin. Five ml of the dissolution medium were withdrawn at various time intervals, filtered though a 0.45 μ nylon disc filter, and replaced with the same volume of fresh dissolution medium. The filtered samples were analyzed for HF · HCl spectrophotometrically at 254 nm. Triplicate dissolution rate determinations were made for each product and average percent of HF · HCl dissolved was plotted versus time.

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BOOK REVIEWS

Wasser, Fasten Luft und Licht – Die Geschichte der Naturheilkunde in Deutschland

Von Uwe Heyll. Frankfurt/New York 2006: Campus-Verlag. 310 S., € 29,90, ISBN 978-3-593-37955-5

Die grundlegenden Arbeiten Carl Eduard Rothschuhs aus dem frühen 1980er-Jahren haben die Historiographie der Naturheilkunde nachhaltig geprägt. Gut zwanzig Jahre später liegt nun eine neukonzipierte, aus einem DFG-Projekt hervorgegangene, umfassende Untersuchung als weitere Gesamtdarstellung des Themas vor, die von den Anfängen bis zu den Auswüchsen im Dritten Reich und die Nachkriegstransformation zur Ganzheitsmedizin reicht. Der Hauptteil des Werkes ist indes der Naturheilkunde im engeren Sinne gewidmet, die mit dem Elementen Wasser, Licht und Luft sowie diätetisch therapiert und weitgehend ohne den Einsatz von Arzneimitteln auskommt. Uwe Heyll zeichnet entsprechend die Entwicklung von den Anfängen im beginnenden 19. Jahrhundert nach, die durch heute noch berühmte Wasserheiler wie Kneipp und Prießnitz, geprägt waren. Dabei gelingt es überzeugend und plausibel, Verbindungen und Verstrickungen, aber auch Besonderheiten und Gegensätze der jeweiligen Schulen darzustellen, die vor allem gegen Ende des 19. Jahrhunderts zutage traten, als die Naturheilkunde als Ganzes in eine sichtliche Identitätskrise geriet. Interessant ist zu sehen, wie aus idealistischen Gedanken Einzelner ganze Volksbewegungen entstanden und teilweise verschwanden, oder im Richtungsstreit ihrer Verfechter zerrieben wurden. Besonders deutlich wird dies anhand der Veröffentlichungen in den einschlägigen naturheilkundlichen Zeitschriften, die offensichtlich sehr gründlich ausgewertet wurden. Besonderes Augenmerk wird auf die kontinuierliche Dialektik zwischen Naturheilkundlern und approbierten Ärzten gelegt, die sich teilweise der Methoden annahmen, sie teilweise aber auch rigoros bekämpften. In der Darstellung derartiger Zusammenhänge und Wechselwirkungen vor dem jeweiligen historischen Hintergrund liegt denn auch die Stärke der vorliegenden Studie; sie beschränkt sich keineswegs auf die Beschreibung der Lebensleistungen einzelner Protagonisten, deren Namen schon allein deshalb geläufig sind, weil nach ihnen ganze Verfahren benannt wurden (Schroth-Kur, Kneipp-Guss etc.), sondern versucht erfolgreich, Entwicklungsstränge zu verfolgen. Insgesamt also ein äußerst lesenwertes und zudem erschwingliches Buch, das sich als maßgebliches Standardwerk neben Rothschuh einen Platz erobern dürfte. Helmstädter (Eschborn)

Chromatographic Methods in Clinical Chemistry and Toxicology

Herausgegeben von Roger Bertholf und Ruth Winecker. New York 2007: J. Wiley and Sons. 308 S., 112,50 €. ISBN 978-0-470-02309-9

Das neue Buch „Chromatographic Methods in Clinical Chemistry and Toxicology“, erschienen im Wiley Verlag, widmet sich auf seinen 308 Seiten dem vielfältigen Einsatz chromatografischer Methoden in der biochemischen Analytik. Nach dem einführenden Kapitel, das den Hintergrund und die Bedeutung der Validierung chromatogaphischer Methoden beschreibt, werden in den folgenden zwölf Kapiteln Einsatzmöglichkeiten der Chromatografie für die Bestimmung von Anabolika, pflanzlichen Nahrungsergänzungsmitteln, L-Dopa und L-Tyrosin als Indikatoren maligner Melanome, Proteinen und Transferrin zur Beurteilung von Alkoholmissbrauch (Kapitel 2–6) beschrieben. In Kapitel 7–13 werden toxikologische Fragestellungen wie die Bestimmung leichtflüchtiger Substanzen mittels Headspace-Chromatografie, die Analytik von Pestiziden, Neurotoxinen, γ-Hydroxybuttersäure und Schwermetallen behandelt. Dabei wird in jedem Kapitel eine kurze Einleitung über den Hintergrund und den derzeitigen Stand der Entwicklung der jeweiligen Fragestellung gegeben sowie Vor- und Nachteile diskutiert. In übersichtlichen Tabellen werden die entsprechenden chromatografischen Methoden mit Literaturangaben zusammengefasst. Das Buch kann deshalb als eine wertvolle Hilfestellung bei der Einarbeitung in die oben genannten Gebiete dienen und erlaubt zusätzlich einen Überblick über den vielfältigen Einsatz chromatografischer Methoden auf dem Gebiet der klinischen Chemie und Toxikologie. In der nächsten Auflage ist ein weiteres Kapitel über das Gebiet der Arzneimittelanalytik und seine Bedeutung für die klinische Toxikologie sehr wünschenswert. Dennoch kann es als interdisziplinäres Fachwerk nicht nur (angehenden) Pharmazeuten, sondern auch Bio-/Chemikern, Biologen, Toxikologen, Ärzten und technischen Mitarbeitern empfohlen werden.

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