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Etodolac-Liquid-Filled Dispersion into Hard Gelatin Capsules: An Approach to Improve Dissolution and Stability of Etodolac Formulation

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ABSTRACT The formation of melt dispersion is an effective method of increasing the dissolution rate of poorly soluble drugs, and hence, of improving the bioavailability. The carrier fusion method was used to prepare different dispersion of etodolac using Gelucire 44/14 and D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS). The physical characteristics of the binary systems were determined by differential scanning calorimetry (DSC), infrared spectroscopy (IR). The release rate from the resulting dispersion was determined from dissolution studies by use of USP dissolution apparatus II (paddle method). The dissolution rate of etodolac is increased in all the dispersion systems compared to that of pure drug. A liquid dispersion system of etodolac (20%) and Gelucire 44/14: TPGS blend (80%), in different ratios, was also prepared. The capsule formulation was subjected to stability studies at different temperature and humidity conditions as per ICH guidelines. Physical and chemical properties of the dispersion didn't change during a period of storage at room temperature and at 4°C, 0% RH. It was found that etodolac was chemically stable against the effects of temperature and humidity. However, the relative humidity and storage time exerted an effect on the dissolution behavior of etodolac. The changes in dissolution behavior after storage under conditions of high humidity and temperature might be related to the formation of etodolac microcrystal and to water absorption by the carrier during storage. It is predicted that acceptable shelf-lives should result when moisture-resistant packaging is used for pharmaceutical formulations of this type.

KEYWORDS Etodolac, Liquid dispersion, Phase solubility study, Gelucire 44/14, TPGS, Dissolution studies, Stability

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INTRODUCTION

The solubility of a drug is an important factor in determining the rate and extent of absorption and thus the appearance and intensity of the therapeutic

effect. Poorly soluble drugs are characterized by a low tendency to dissolve in the aqueous fluids of the administration environment. After their oral administration, this results in poor bioavailability. To overcome these problems many chemical and formulation approaches aim to improve the release rate of poorly soluble drugs. Chemical approaches are mainly based on the formation of soluble prodrugs or salts. Formulation approaches are mainly based on the use of polymorphous (Henck, 1997) or amorphous (Hancock & Zografi, 1997) forms of the drug, complexation, a decrease of particle size and drug dispersions in soluble solid carriers. Drug dispersions are now receiving increasing attention for their easy preparation, the possibility to use a wide range of carriers, and their suitability for any drugs.

An extensive review of selection of suitable carriers has been presented by Ford (1980). In addition to water soluble carriers with no intrinsic solubilizing properties such as high molecular weight polyethylene glycols (PEG) and polyvinylpyrrolidones (PVP), the use of lipid-based amphiphilic carriers with solubilizing properties like Gelucire 44/14 and TPGS has recently attracted much interest (Serajuddin, 1994; Yüksel et al., 2003; Prasad et al., 2003). Gelucire 44/14 is a saturated polyglycolized glycerides consisting of a well-defined mixture of mono-, di-, and tri-glycerides and mono- and di-fatty acid esters of polyethylene glycol. It has a melting temperature of 44°C and a hydrophilic-lipophilic balance (HLB) value of 14, hence its name (Roussin & Laforet, 1997; Gattefossé, 1999). TPGS (D-α-tocopheryl polyethylene glycol 1000 succinate) is a water soluble derivative of Vitamin E consisting of a hydrophilic polar head group (polyethylene glycol) and a lipophilic tail (tocopherol succinate) resulting in amphiphilic properties, HLB value = 13.2 (Eastman Chemical, 1998; Wu & Hopkins, 1999). TPGS has a relatively low critical micelle concentration of 0.02 wt.% above which this carrier offers the advantage of spontaneously solubilizing lipophilic drugs upon contact with an aqueous medium to form a fine emulsion that, in turn, further facilitates drug absorption. TPGS has a relatively low melting temperatures range of 37–41°C. Postprandial "food effect" (increase in bioavailability) might be another advantage offered by these lipid-based formulations (Khoo et al., 2000).

The most widely described method of dosage form production employing such hydrophilic carriers is the liquid filling of hard gelatin capsule, whereby the drug and the lipid base are heated to the molten state and filled into the capsule shell, whereupon the materials are allowed to cool and solidify. There have, however, been a number of alternative approaches described in the literature, including the use of melt extrusion (Pinto & Silverio, 2001), the preparation of hydrogels (Martin et al., 2002), spray-congealing using ultrasound (Passerini et al., 2002), and the use of supercritical fluid technology to produce Gelucire coat on drug–loaded particles (Thies et al., 2003). A number of studies have been performed on the properties of the bases, examining issues such as the effect of cooling rate on the thermal properties of lipid (Sutananta et al., 1994a, 1994b), and the solidification properties of Gelucire 44/14 (Dordunoo et al., 1996).

Etodolac (1,8-diethyl-1,3,4,9-tetrahydropyrano [3,4–6]indol-1-yl) acetic acid is a nonsteroidal anti-inflammatory agent; with potent antiarthritic activity (Balfour & Buckley, 1991). It is used usually at an oral dose of 200 mg twice daily; up to 600 mg daily may be given if necessary. The drug has a very poor solubility in water that limits its use to solid dosage form for oral administration. Its bioavailability is expected to be limited by its dissolution rate, which might be increased using solid dispersion technology.

The aim of the present work was to prepare and characterize different dispersions of etodolac with Gelucire 44/14 and TPGS so as to improve its dissolution properties. In order to evaluate the effect of these carriers on etodolac, dissolution and solubility studies were performed. Representative sample was stored at different conditions according to ICH guidelines to monitor the physical stability of the dispersion.

EXPERIMENTAL

Materials

Etodolac was obtained from Pharco Co, Cairo, Egypt. Gelucire 44/14 was obtained as a gift from Gattefossé Corporation, Saint-Priest-Cedex, France. D-α-tocopheryl polyethylene glycol 1000 succinate was obtained from Peboc Division of Eastman Chemical (UK) Limited (United Kingdom). Hard gelatin capsule shell size, 1 and 0, was obtained from Spimaco Co, El Qassim Pharmaceutical Plant. All organic solvents were high-performance liquid chromatography (HPLC) grade. All other chemicals were of analytical grade.

Methods

Solubility Study

Solubility studies were performed according to a published method (Higuchi & Connors, 1965). An excess amount of pure etodolac was placed into each 20 mL scintillation vial, to which were added 10 mL of water containing various concentration of increasing amount of Gel 44/14 or TPGS (5–30%). The sealed vials were sonicated for 1 h at room temperature (Grant Ultrasonic bath, Cambridge Ltd; England). Thereafter, the vials were agitated in a thermostated shaking water bath set at 37°C ± 0.1 or 45°C ± 0.1 for 48 h (Karl Kolb, Buchschlag, Germany). After 2 days, an aliquot of each mixture was transferred to a 10 mL glass syringe preheated at the appropriate temperature filtered through a 0.45 μm membrane filter (Millipore Cellulose Acetate) in thermostatic test tubs. About 1 mL of the clear filtrate after appropriate dilution, were allowed to stand in bath at appropriate temperature until analyzed. Concentration of Etodolac in each aliquot was determined spectrophotometrically at 277 nm with reference to a suitable constructed standard curve. All of the manipulations were made without the removal of the vial from the water bath, using thermostated pipettes, syringes. ALL Gelucire 44/14 solutions were diluted with methanol. The apparent stability constants, Ks, were calculated from the phase solubility diagrams with the assumption of 1:1 stochiometry, according to the equation

$$Ks = \frac{\text{slope}}{So \infty (1 - \text{slope})} \quad (1)$$

where So is etodolac solubility in the absence of carrier.

Preparation of Etodolac Dispersion

Accurately weighed amounts of either Gelucire 44/14 or TPGS were placed in an aluminum pan on water bath and melted, with constant stirring with a glass agitator, at 60°C. Fusion was reached in 20 min at this temperature. An accurately weighed amount of etodolac (in ratio 1:1; 1:2; and 1:4 etodolac : carrier) was incorporated into the melted carrier with stirring to ensure homogeneity. The mixture was heated until a clear homogeneous melt was obtained.

Manufacture of the Capsule Formulation

The above process was followed to the point of agiatation and the molten mixture either semi-solid or liquid form was filled into the bodies of size 1 or 0 capsules using medicine droppers. These were then allowed to cool for 2 h before being capped. The fill weight of the capsules was 200–500 mg, containing 100 mg etodolac. The filled capsules were stored at room temperature until testing; homogeneity was indicated by the excellent reproducibility of the DSC data. Following preparation of the solid dispersion, the chemical stability of etodolac was determined by HPLC to ensure that the drug had not undergone chemical decomposition during the fusion process. It was noted that no leakage or visible change in appearance was apparent during the time of storage under ambient temperature.

Fourier Transform Infra-Red (FT-IR) Spectra

The spectra were recorded on Perkin Elmer 2000 FT-IR system (Perkin-Elmer, Norwalk, CT, USA). Infrared (IR) spectroscopic analysis was carried out on the dispersion to evaluate possible interactions between the drug and the carrier. Samples were prepared by KBr disc method (2 mg sample in 100 mg KBr) and examined in the transmission mode. KBr tablets were prepared at a pressure of 10 tons. Individual polymer, Etodolac and drug/polymer dispersion were run as controls. Scan was obtained at a resolution of 2 cm^{-1}, over a frequency range of 4000 to 400 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry measurements were carried out using a Perkin Elmer DSC-7 differential scanning calorimeter (Perkin-Elmer, Norwalk, CT, USA) equipped with a liquid nitrogen subambient accessory. The instrument was operated under nitrogen purge at a rate of 20 mL/min. All accurately weighed samples (5 mg) were placed in sealed aluminum pans. Thermograms were obtained at a heating rate of 5°C/min, over a temperature range of 25–200°C. An empty aluminum pan was used as reference. Peak temperature, onset, and enthalpy of fusion were determined for all samples. Calibration of temperature and heat flow was performed with indium.

Dissolution Studies

Dissolution studies were carried out in triplicate (one capsule per vessel, each contain 100 mg etodolac) with an Erweka DT600 dissolution test (Erweka, Germany) in 900 mL simulated gastric fluid prepared without pepsin and simulated intestinal fluid (without enzyme) maintained at 37 ± 0.5°C using the paddle apparatus fixed at a rotation speed of 50 rpm. Samples of 3 mL were withdrawn at various time intervals and filtered through a 0.45 μm filter. The volume in the vessel was immediately replaced with fresh dissolution medium maintained at the same temperature. The formulations were assessed visually according to the final appearance of the emulsion formed. The corresponding concentration of etodolac was determined from the calibration curve made from standards of known concentration. The amount of Etodolac was determined spectrophotometrically at 277 nm (Ultrospec 2100 Pro, UV/Visible Spectrophotometer) without interference from Gelucire or TPGS. Dissolution tests were carried out for 120 min. The results presented are mean values of three determinations. Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time (Khan, 1975). The mean dissolution time (MDT) was employed for comparison of dissolution profiles, (Polli et al., 1997) calculated as

$$MDT_{\text{in vitro}} = \frac{\sum^{n} i=1 \quad t_{mid} \quad \Delta M}{\sum^{n} i=1 \ \Delta M} \qquad (2)$$

where i is the dissolution sample number, n is the number of dissolution sample times, t_{mid} is the time at the midpoint between times t_i and t_{i-1}, and Δ M is the amount of drug dissolved between t_i and t_{i-1}.

Stability Studies

It was established that glycerid-based products may exhibit aging effects, whereby a range of physical properties may change on storage of the bases which are sometimes accompanied by changes in the in vitro, in vivo release of drug from the dosage form. Etodolac dispersion containing 20% etodolac and 80% mixture of Gelucire 44/14 and TPGS in ratio 1:1 was selected for stability on the basis of the in vitro drug release profile. The optimized formulation capsules were stored in glass bottles (unpacked capsules) and subjected to accelerated stability studies as per ICH guidelines i.e. 25°C/0% RH, 4°C, 0% RH, 25°C/60% RH and 40°C/75% RH (Grimm, 1998). The desired RH was achieved by putting samples into airtight glass container with silica gel (0% RH) or a saturated solution of salt prepared beforehand. The containers were placed inside ovens in order to control the temperature. At defined intervals of time, the samples were removed from the desiccators and weighed. The samples were recovered during weighing to reduce direct exposure to the external atmosphere. After the period of time (≈36–62 h) required for apparent sorption equilibrium, as evidenced by constant weight, the samples were subjected to DSC to detect any phase change due to water sorption. Sampling was done at predetermined time intervals of 0, 2, 4, 6 months. Capsules were evaluated for the appearance, drug content and in vitro release. A simple sensitive and stability indicating HPLC method was developed and validated for content analysis during accelerated stability studies (Ficarra et al., 1991). The HPLC system consisted of a Shimadzu HPLC pump equipped with a Shimadzu detector. The column used was C_{18} (150 mm × 4.6 mm, 5 μ particle size), the mobile phase consisted of acetonitrile: potassium dihydrogen orthophosphate (0.04 M, pH 6.0), 30:70 at a flow rate 1.5 mL/min. Analysis was done at a wavelength of 276 nm.

RESULTS AND DISCUSSION

Chemical Characterization of Etodolac Dispersion After Preparation

The chemical stability of etodolac during the fusion process was determined by HPLC assay. The assay was tested for accuracy, linearity and sensitivity. The correlation coefficients of the calibration curves (greater than r = 0.9967) confirm good linearity in the range of 0.5 μg/ml–20 μg/ml). The area of the etodolac in the HPLC chromatograms of samples taken from all the final formulations accounted for greater than 99.4 of the total peak area. This proved to be in good agreement with the theoretical values. The absence of other peaks indicates that etodolac didn't undergo chemical decomposition during the fusion process or appear to have interacted with the carriers.

Phase Solubility Studies

The solubility of pure etodolac in water is poor, but the literature gives no exact data. In this study the solubility of etodolac in water was found to be about 75 μg/mL. Figure 1 shows the solubility phase diagram representing the effect of increasing the concentrations of Gelucire 44/14 and TPGS on the apparent solubility of etodolac in water at 37°C and 45°C. Comparing the two polymers, aqueous solutions of TPGS increased the solubility of etodolac more than that of Gelucire 44/14. Solubility experiment showed that the concentration of Etodolac in water at 37°C, 45°C increased as a function of Gelucire or TPGS concentration. The increase in solubility was linear with respect to the weight fraction of the carrier. The shape of all solubility diagram followed an A_L-type system (Higuchi & Connors, 1965) where a linear increase of etodolac solubility was observed as function of Gelucire, TPGS concentrations, over the entire concentration range studied. At 15% concentration of Gelucire 44/14 and TPGS, the increase in etodolac solubility was approximately 22– and 27–fold, at 37°C, respectively, and 37-fold for Gelucire 44/14 at 45°C. The apparent solubility constant ($k_{1:1}$) were estimated from the slope of the straight line of the phase-solubility diagram according to equation (1). The stability constant values vary with the carrier (129 and 161 g^{-1} for Gelucire 44/14 at 37°C and 45°C, respectively, and 171 g^{-1} for TPGS at 37°C). The increase in solubility of etodolac by Gelucire 44/14 and TPGS may probably be explained by increased wettability of etodolac and micellar solubilization. Indeed, Gelucire and TPGS being surfactants cause a decrease of the interfacial tension between the drug and the dissolving solution. The same effect of Gelucire 44/14 was observed for the solubility of temazepam at 37°C (Dordunoo, 1991) and halofantrine (Khoo et al., 2000).

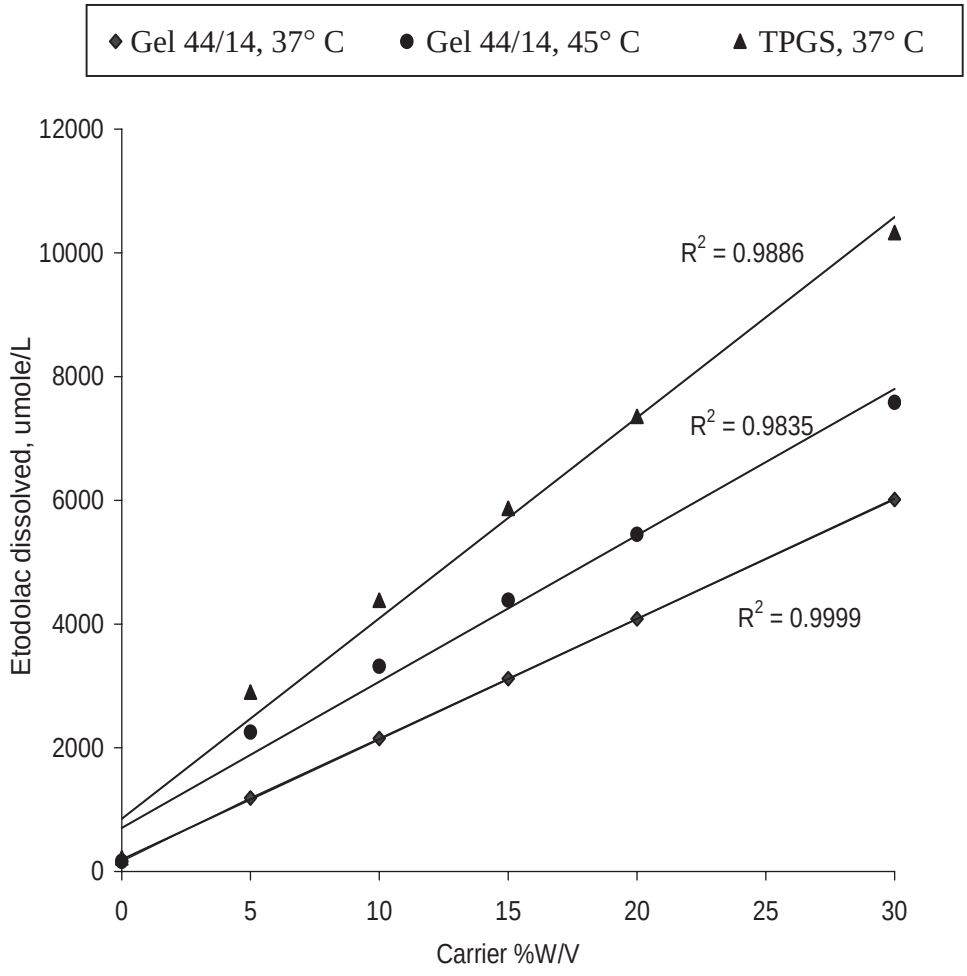

FIGURE 1 **Phase-Solubility Diagram of Etodolac in the Presence of Increasing Concentration of Gelucire 44/14 and TPGS in DI-Distilled Water at Different Temperature.**

TABLE 1 **Thermodynamic Parameters of the Solubility Process of Etodolac in Water-Gelucire 44/14 and Water- TPGS Systems at Different Temperature**

%Carrier concentration	Gelucire 44/14 ΔG°_{tr} (kJ/mole)		TPGS ΔG°_{tr} (kJ/mole)
	37°C	45°C	37°C
5	–3.875	–6.661	–5.644
10	–4.902	–6.758	–6.026
15	–6.221	–7.421	–6.986
20	–7.128	–8.595	–7.879
30	–7.835	–9.191	–8.453

Table 1 presents the thermodynamic parameters associated with the aqueous solubility of Etodolac in the presence of Gelucire 44/14 or TPGS. An indication of the process of transfer of Etodolac from pure water to the aqueous solution of Gelucire or TPGS may be obtained from the values of Gibbs free energy (ΔG°_{tr}) of transfer of etodolac from pure water to the aqueous Gelucire or TPGS solution may be calculated as follows

$$\Delta G^\circ_{tr} = -2.303\, RT \log So/S$$

where So/S is the ratio of the molar solubility of etodolac in aqueous solution of Gelucire or TPGS to that in pure water. The data provide the information regarding the increase of solubility of Etodolac in the presence of Gelucire or TPGS. ΔG°_{tr} values were all negative indicating the spontaneous nature of drug solubilization, and it decreased with increase in the Gelucire or TPGS concentrations demonstrating that the reaction became more favorable as the concentration of Gelucire or TPGS increased.

Several mechanisms have been proposed to account for the increase in the dissolution kinetic of drug from solid dispersion. These mechanisms include the carrier controlled dissolution (Corrigan et al., 1979; Dubois & Ford, 1985; Craig & Newton, 1992), the continuous drug layer formation (Dubois & Ford, 1985) that involving the release of intact particles with dissolution occurring over a large surface area (Saers Sjökvist & Craig, 1992). The later mechanism has been suggested to be important at low drug levels. It is also clear that a modification of the surface properties and hence a reduction of the contact angle value improves the wettability of the powder and it should lead to an increase of dissolution rate. Van den Mooter et al. (1998) suggested that an improvement of wettability of the powder could results from the formation of a film of PEG around the drug substance particles which modify the hydrophobicity of their surfaces.

FTIR Spectroscopy

The interaction between the drug and the carrier often leads to identifiable change in the IR profile of the solid dispersions. Etodolac and the dispersions were subjected to IR analysis in order to evaluate possible interactions between the drug and the carrier. The data was compared with the standard spectrum for etodolac, and characteristic peaks associated with specific structural characteristics of the molecule and their presence/absence in the polymeric carrier as well as the dispersion were noted. This was expected to provide information regarding the specific structural features of the drug molecule interacting with the excipients used. The representative IR spectra are shown in Fig. 2. Etodolac, which is present as ether forms, showed the C-O stretching vibration at 1037 cm^{-1}. Other characteristic bands are shown at 1740 cm^{-1} for C = O stretching vibration of the COOH group, at 3530 cm^{-1} for N-H stretching vibration of secondary amine group and at 3720 cm^{-1} for free O-H stretching vibration of the COOH group. The stretching band in the region of 3500–3200 cm^{-1} assigned to the non-bonded aromatic imino group was not shown in the spectrum of the semi-solid dispersion. Therefore, it is presumed that the dispersion shows an interaction such as association between the functional group of etodolac and the water soluble polymers. An association between etodolac and Gelucire 44/14 or TPGS is expected to be most probable between the imino group of etodolac and the carboxyl group of Gelcuire 44/14 and TPGS.

Thermal Analysis (DSC)

The DSC thermograms of pure etodolac, neat Gelucire 44/14, neat TPGS and the dispersion over the temperature range from 25–200°C are shown in Fig. 3. Pure etodolac exhibits a sharp melting endotherm at 157.8°C corresponding to the melting point of the drug (Fig. 3A). The thermograms of TPGS and

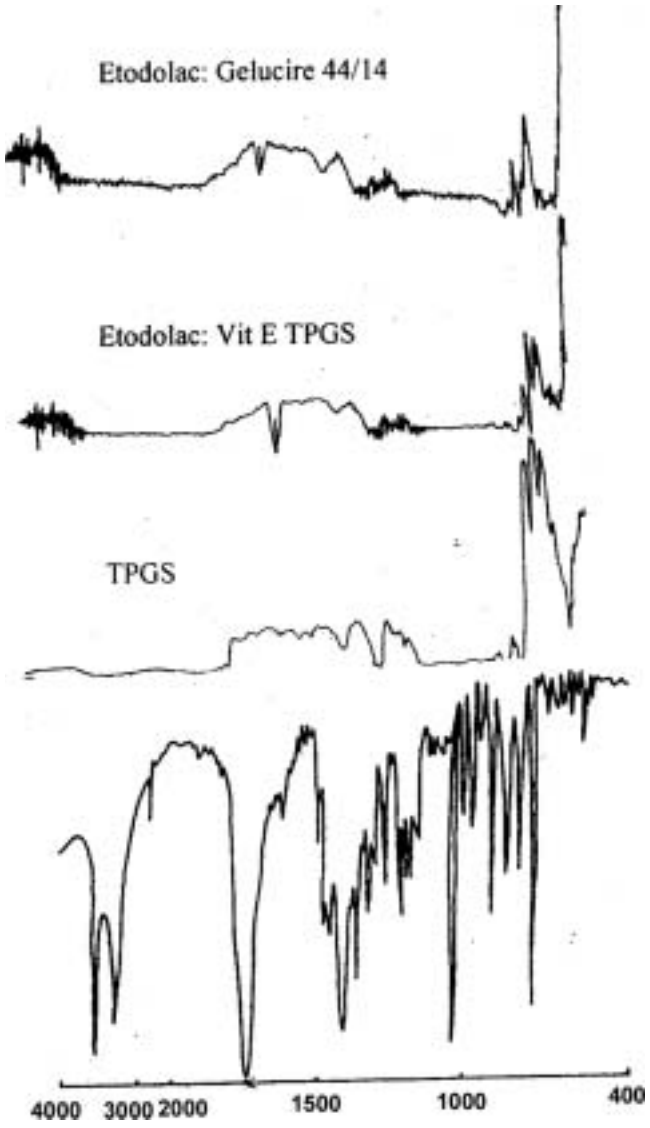

FIGURE 2 **FT-IR Spectra of Etodolac, TPGS, Etodolac: TPGS, and Etodolac: Gelucire 44/14.**

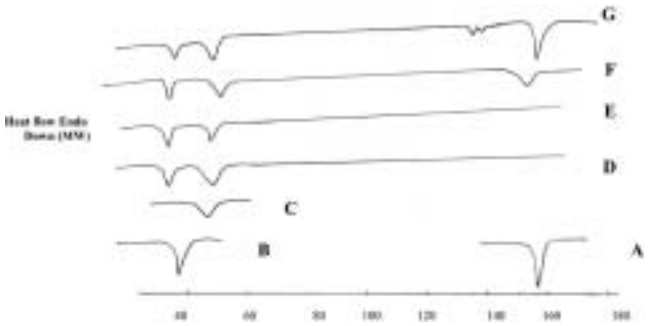

FIGURE 3 **DSC Thermograms of A) Pure Etodolac; B) Pure TPGS; C) Pure Gelucire 44/14; D) Etodolac-Free Dispersion; E) Etodolac-Loaded Gelucire 44/14: TPGS, 1:2:2; F) Etodolac : Gelucire 44/14: TPGS Liquid Dispersion After Storage at 25°C/ 65% RH for 6 Months; G) Etodolac : Gelucire 44/14: TPGS Liquid Dispersion After Storage at 40°C/ 75% RH for 6 Months.**

Gelucire 44/14 (Fig. 3B and C) showed a single endothermic peak corresponding to their melting point; TPGS (38.7°C) and Gelucire 44/14 showed a broad melting endotherm at 47.6°C. The broadness of Gelucire 44/14 peak was arising from the segregation of Gelucire components into fraction with different melting points (Sutananta, et al., 1994a). The drug–free dispersion exhibited a sharp endotherm at 36.8 and a small at 44.1 (Fig. 3D). The sharp melting endotherm observed indicate the partial crytallinity of this drug-free dispersion. Sutananta et al. (1994b) have shown that the glycerides present in Gelucires exhibit complex crystallization behavior, which may affect the product performance of the dosage forms. Also, the melting point of both Gelucire 44/14 and TPGS decreased after preparation of the melt dispersion, suggesting the formation of a eutectic. The same phenomenon has been previously reported (Damian et al., 2000). The liquid etodolac dispersion showed two melting endotherm: a sharp one at 36°C and a small broad one at 42°C (Fig. 3E). The decrease in peak melting temperature of lipid matrix due to presence of drug was always less than 2–4°C. No endotherm corresponding to the melting of pure crystalline etodolac was observed. These results suggest that on heating in DSC, etodolac progressively dissolve in Gelucire and TPGS and dissolve completely below the melting temperature of crystalline etodolac. This indicates that formation of an amorphous dispersion, the molecular encapsulation of the drug inside the Gelucire 44/14 and TPGS. Even after 6 months of storage of etodolac dispersion in vacuum desiccator at 4°C or at room temperature, no endothermic peaks were detected around the melting point of etodolac. Other dispersions have been found to behave similarly. Example include the solid dispersion of triamterene in PEG and Gelucire 44/14, in which triamterene forms monotectics with both polymers (Dordunoo et al., 1991); the solid dispersion of cinnarizine in Gelucire 53/10, in which no melting peak of cinnarizine was observed at low concentration (≤30% w/w) (Ginés et al., 1995); and the solid dispersion of paracetamol in PEG 4000, were again there was evidence of monotectic behavior (Lloyd et al., 1997). Craig (1990) has previously suggested that the drug may dissolve in the molten polymer, such as PEG, over a wide range of temperature; hence the melting endotherm of the drug broaden to such an extent as to be

indistinguishable from the baseline. The data presented here largely supports this hypothesis.

Dissolution Studies

Gelucire 44/14 and TPGS were chosen as the hydrophilic polymers for the present studies as these highly water soluble and non-toxic polymers are known to enhance dissolution rate of insoluble drugs. Etodolac dispersion containing a unit dose of 100 mg etodolac in a solubilizing matrix comprising either Gelucire 44/14, TPGS or combination thereof were prepared for in vitro evaluation. The dissolution studies were conducted in either an acidic (0.1 NHCL) or neutral phosphate buffer (pH = 6.8) solution to encompass the range of likely pH values encountered in the GIT. The solubility of etodolac in purified water is 75 μg/mL, and this level was not achieved within 120 min. In both acidic and neutral media, the dissolution of etodolac from the powder alone was incomplete during 120 min. All the binary systems with either Gelucire 44/14 or TPGS displayed better dissolution properties with respect to etodolac alone. Etodolac being a weakly acidic drug having pKa of 4.65, all preparation showed higher concentration of dissolution in intestinal fluid when compared with the gastric fluid (data not shown). The increase in solubility of etodolac by Gelucire 44/14 and TPGS can be probably be explained by increased wettability and micellar solubilization seems more logical as both carriers being surfactants cause a decrease in the interfacial tension between etodolac and the dissolving solution. A similar increase in the solubility of other drugs by Gelucire 44/14 has been reported (Dordunoo et al., 1991). The results of the dissolution efficiencies at 120 min (DE_{120}) and MDT of various etodolac dispersion formulations are collected in Table 2.

All the dispersion exhibited significant faster initial dissolution rate than the pure drug. Serajuddin et al., (1988) and Smith et al., (1990) showed that Gelucires with high HLB values may be used to obtain fast release of drugs. Increasing the proportion of solubilzing carrier to drug and hence the self-emulsifying efficiency of the formulation, resulted in an improvement in the drug solubilization and in the visual grading of the emulsions formed. In these studies, TPGS appeared to have slightly better solubilzing properties than Gelucire 44/14. For example, at all ratios of etodolac: TPGS, formation of clear microemulsion in both acidic and neutral medium was obtained, whereas etodolac: Gelucire formulations required higher proportion of carrier (1:4) to produce similar results. In an attempt to reduce the amount of TPGS incorporated into the formulation, formulations containing both Gelucire 44/14 and

TABLE 2 **Dissolution Parameters* of Various Formulations of Etodolac/Gelucire 44/14 and TPGS Dispersions**

Sample	% Carrier concentration	DE_{120}[a] (%)		MDT (min)[b]		DP_{60}[c]	
		0.1 N HCL	Buffer, pH 6.8	0.1 N HCL	Buffer, pH 6.8	0.1 N HCL	Buffer, pH 6.8
Etodolac	–	17.5	41.2	>120	60.0	28.0	51.5
Etodolac-Gelucire 44/14							
1:1	50%	26.9 ± 3.2	50.5 ± 2.7	>120	45.2 ± 2.9	36.5 ± 3.0	62.5 ± 3.7
1:2	66.6	48.7 ± 5.7	61.8 ± 4.7	45.2 ± 3.9	25.5 ± 3.9	61.1 ± 1.9	71.3 ± 2.4
1:4	80	79.9 ± 2.7	81.9 ± 6.8	20.1 ± 2.9	12.5 ± 1.1	96.4 ± 3.2	103.7 ± 4.6
Etodolac: TPGS							
1:1	50%	37.8 ± 4.7	54.6 ± 5.7	90.3 ± 6.5	40.8 ± 4.9	48.9 ± 5.8	61.9 ± 4.8
1:2	66.6	57.9 ± 2.9	74.8 ± 4.6	40.1 ± 4.9	20.5 ± 4.7	74.5 ± 6.0	98.7 ± 3.7
1:4	80	82.4 ± 3.5	89.2 ± 2.8	20.6 ± 3.2	11.4 ± 1.0	104.2 ± 5.2	105.2 ± 2.9
Etodolac: Gelucire 44/14: TPGS							
1: (3:1)	80	90.9 ± 4.8	92.6 ± 4.7	8.1 ± 2.3	5.3 ± 4.1	102.3 ± 4.8	103.8 ± 4.7
1: (2:2)	80	89.7 ± 3.8	95.4 ± 2.7	5.3 ± 1.8	5.5 ± 3.2	104.5 ± 5.9	101.3 ± 5.7
1: (1:3)	80	91.3 ± 4.7	94.4 ± 3.8	8.7 ± 2.8	5.0 ± 1.9	103.7 ± 3.7	102.4 ± 4.9

*Results represent means of replicate determinations with the standard deviation (n = 3).

[a]Dissolution efficiency calculated from area under the dissolution curve at t = 120 min expressed as % of the area of the rectangle described by 100% dissolution in the same time (average of three determination, coefficient of variation CV < 7%).

[b]Mean dissolution time is calculated according to Eq. 1.

[c]Percentage of drug dissolved after 60 min.

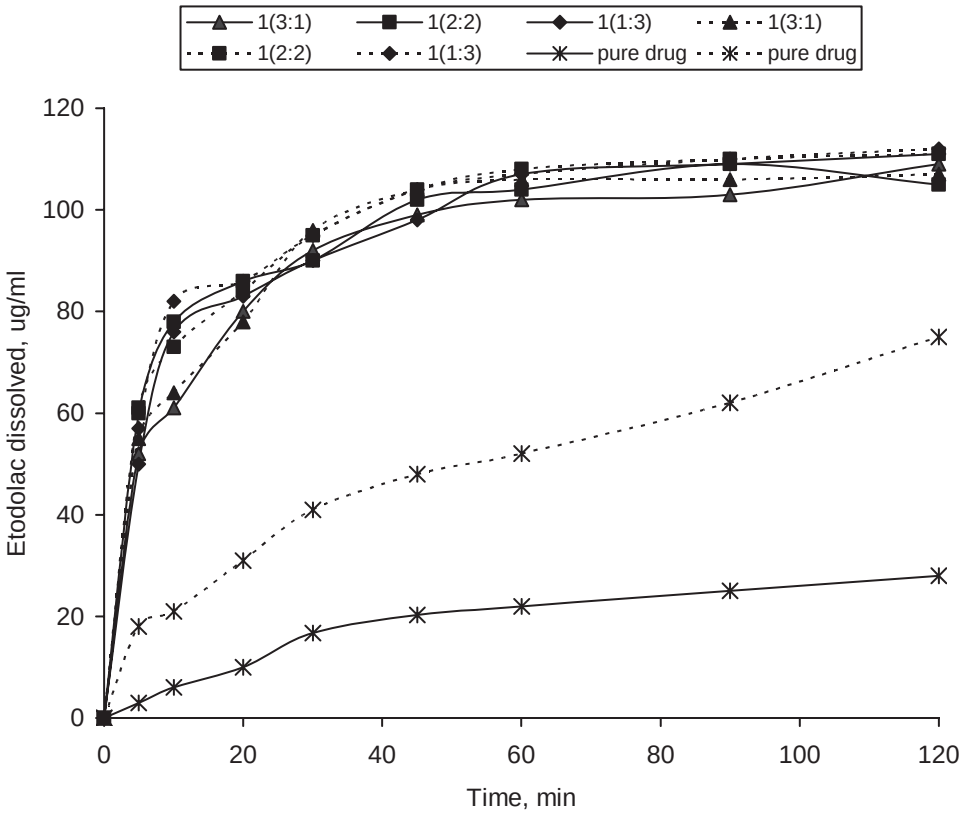

FIGURE 4 **Dissolution Profiles of Pure Etodolac and Etodolac: Gelucire 44/14: TPGS Dispersion at 37°C in 0.1 N HCl (solid line) and Phosphate Buffer, pH 6.8 (dotted line). Data are the Mean of Three Determinations.**

Vitamin E TPGS in varying proportions were studied (Fig. 4). The three ternary mixture of etodolac: Gelucire 44/14: TPGS provided faster release than individual lipid material in both dissolution media. Not less than 90% of etodolac was released within 30 min. MDT was less than 10 min for all formulation, the dissolution efficiency after 120 min (DE_{120}, %) were ranged from 89.7–95.4 in both dissolution medium.

Effect of Temperature and Relative Humidity on the Physical Stability of Etodolac Dispersion

For the stability study, one of the dispersion (etodolac: Gelucire 44/14: TPGS, 1:2:2) was investigated after storage for 2, 4, and 6 months under different conditions. In freshly prepared formulation, etodolac is present in the amorphous form and the DSC patterns display no peaks that can be attributed to etodolac crystals either before or after storage at room temperature or at 4°C/0% RH, suggesting that crystallization doesn't occur in this case. No new peaks, no change in the thermogram of the dispersion after storage under these condition (data not shown) indicating that neither the drug nor the matrix system underwent any phase change. Also, chemical stability of the active ingredient improved to be unchanged upon aging of the capsule formulation during the period of the study which is confirmed by HPLC assay.

While glycerides and Vitamin E are not in themselves hygroscopic, the presence of the PEG part in the Gelucires and in TPGS may facilitate an interaction with water. Upon exposure of the capsule formulation to 65% RH at 25°C or 75% RH at 40°C, The maximum water uptake are found to be 2.46% and 6.80%, and they are achieved after ≈ 62 and ≈ 36 h, respectively. The equilibrium moisture uptake and the rate of its attainment are greater after exposure to high humidity at 40°C than after exposure to less humidity at 25°C. Water uptake for etodolac dispersion may be attributed to the greater proportion of the carrier (80%), which can form hydrogen bond with water molecules sorbed from the vapor. Following the

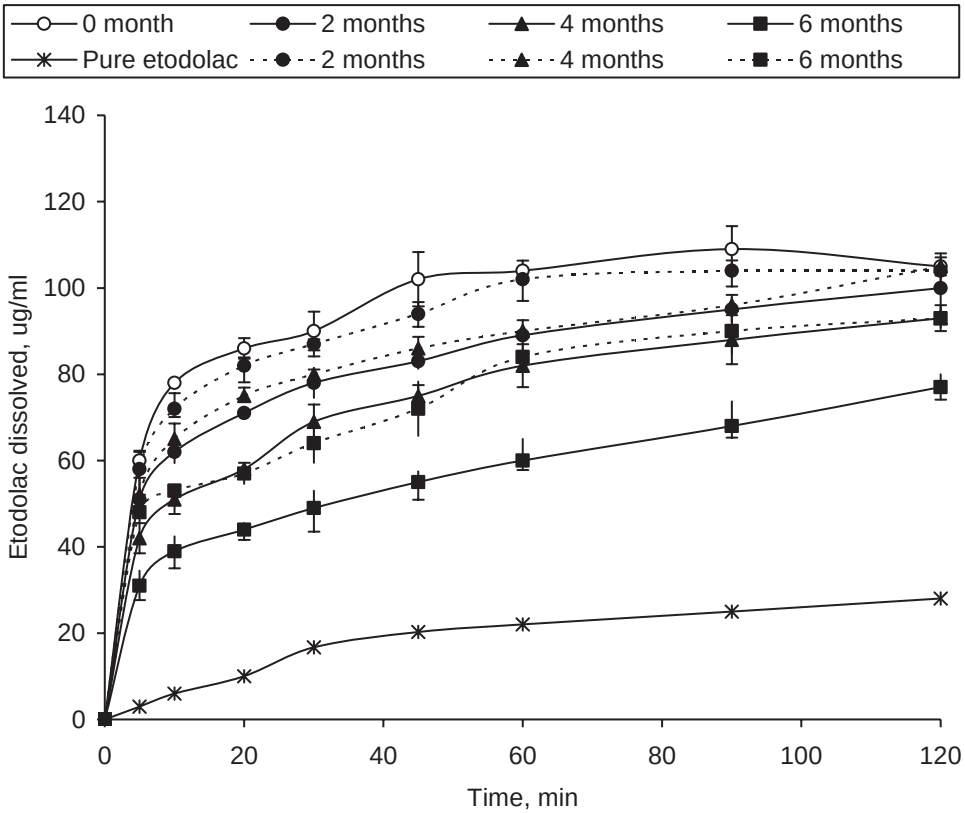

FIGURE 5 **Dissolution Profiles of pure etodolac and etodolac: Gelucire 44/14: TPGS dispersion (1:2:2) in 0.1 N HCL, freshly prepared sample and after storage at 2, 4 and 6 months at 25°C/ 65% RH (dotted line) and 40°C/ 75% RH (solid line). Data are the mean of three determinations.**

maximum water uptake, a loss in weigh was observed for all samples, as a result of some leakage from the capsules during preliminary stability testing at 40°C. This behavior suggests that the ingredients in the dispersions are crystallizing on uptake of water. It is therefore possible that the presence of moisture in the dispersions facilitates the segregation process of the carrier resulting in crystallization of the drug and the carrier. A study of the solid dispersions of theophylline in Gelucire base has shown that Gelucires undergo structural alterations on exposure to high humidity, the extent of the changes being highly dependent on the chemical composition of the base (Sutananta, et al., 1996). Another possibility is that a structural change in Gelucire takes place during storage (Doelker, et al., 1986; Laine et al., 1988). The physical stability of the examined formulation was monitored using DSC (Fig. 3F and G). The appearance of the melting peak of etodolac at 155.7°C confirms the crystallization of the drug upon storage at high humidity conditions. It is clear that the dissolution properties deteriorate upon storage at 25°C/60% RH and 40°C/75% RH (Fig. 5). There is a clear relation between this dissolution study and the calorimetric results: the extent to which the dissolution properties deteriorate is linked to the crystallinity of the drug. Both profiles are characterized by a slow dissolution rate. It is however, clear that the dissolution properties are still much better than those of the pure drug. The percent of etodolac dissolved at 1 h from the liquid dispersion, was reduced from 94.6 to 83.7 and to 59.1 upon storage of the capsule formulation for 6 months at 25°C/65% RH and 40°C/75% RH, respectively. The reduction in the dissolution rate suggests that there is a change in the physical structure of the amorphous form of the drug, which is also reflected by water evaporation endotherm in the DSC curves observed. Increasing relative humidity should promote recrystalization by favoring the uptake of water, thereby enhancing molecular mobility (Hancock & Zografi, 1997), (Fig. 3G).

Several studies have examined the drug release properties of the Gelucires basis with many investigation attempting to relate the physical and chemical

properties of the Gelucires to the dissolution rate (Howard & Gould, 1987; Bodmeier et al., 1990; Sutananta et al., 1995; Equisabel et al., 1996). It was concluded that lipid excipients composed of triglycerides can undergo polymorphic transitions, precipitation or crystallization with time, accompanied by corresponding changes in their properties and in rate of release of the formulated active principles (Laine et al., 1988). Amorphous to crystalline conversions are observed, the kinetics of which are found to be both temperature and relative-humidity dependent.

Some products formulated with Gelucire have been found to exhibit aging effect. Remunan et al. (1992a, 1992b) noted a decrease in the dissolution rate of nifedipine from tablets containing nifedipine-PVP complex (90%) and Gelucire 53/10 (10%) during storage from 3 to 6 months at high relative humidity storage condition. In contrast, Dennis et al. (1990) found that the time for 50% ketoprofen release from mixture of Gelucire 50/13 and 50/02 in vitro was reduced from 253 min directly after manufacture to 161 min after 28 days storage at 30°C. Nonetheless, no statistically significant changes were observed in vivo. Indeed, previous studies by Dennis (1988) demonstrated an increase in the melting points of a number of Gelucires (33/01, 46/07, 50/13) on storage, although there was no clear correlation with drug release rate. Other studies showed no change in properties with time (Dordunoo et al., 1991), while other studies have shown no changes in the properties of Gelucire formulation as a function of time (Dordunoo et al., 1991; Dennis, 1988).

Since it is generally assumed that there is some kind of correlation between the dissolution curve of immediate release dosage forms obtained in an in vitro study and the oral absorption/bioavailability in an in vivo situation. This would imply that a range of the dissolution properties of the dispersions upon storage can potentially lead to a reduced uptake of the drug from the gastrointestinal tract. Hence, when developing a drug-dispersion system one should perform a stability study to elucidate which conditions result in no or only a minor decrease of its physical structure in order to stay within the limits of the specification for the dissolution of the dosage form. In this case, storage at conditions of low humidity might be adequate to store such formulation.

A bioavailability indicating in vivo study of this formulation was also performed on rabbits and the results confirming the importance of enhancing dissolution of the drug for increasing in vivo absorption were demonstrated (Barakat, 2006).

CONCLUSION

The present results of investigation show the suitability of Gelucire 44/14, TPGS as the carrier for preparation of etodolac dispersion filled into hard gelatin capsules. As mentioned above, these substances are widely used as pharmaceutical excipient. The amorphous etodolac: Gelucire 44/14 or Vitamin E TPGS dispersion were formed at different ratios. The dissolution rates of etodolac dispersions were higher than that of pure drug; this was possibly caused by the increase in drug wettability. Storage at relatively high temperature and humidity led to crystallization of the drug.

REFERENCES

Balfour, J. A., & Buckley, M. T. (1991). Etodolac A reappraisal of its pharmacology and therapeutic use in rheumatic diseases and pin status. *Drugs 42*, 274–299.

Barakat, N. S. (2006). Enhanced oral etodolac absorption and the anti-inflammatory effect using Gelucire 44/14 and vitamin E-TPGS dispersion. *Bull. Fac. Pharm.* Cairo Univ. In press.

Bodmeier, R., Paeratakul, O., Chen, H., & Zhang, W. (1990). Formulation of sustained release wax matrices within hard gelatin capsules in a fluidized bed. *Drug Dev. Ind. Pharm. 16*, 1505–1519.

Craig, D. Q. M. (1990). Polyethylene glycols and drug release. *Drug Dev. Ind. Pharm. 16*, 2501–2526.

Craig, D. Q. M., & Newton, J. M. (1992). The dissolution of nortiptyline hydrochloride from PEG solid dispersions. *Int. J. Pharm. 78*, 175–182.

Corrigan, O. I., Murphy, C. A., Timoney, R. F. (1979). Dissolution properties of polyethylene glycol and PEG-drug systems. *Int. J. Pharm. 4*, 67–74.

Damian, F., Blaton, N., Naesens, L., Blazarini, J., Kinget, R., Augustijns, P., & Van den Mooter, G. (2000). Physicochemical characterization of solid dispersions of the antiviral agent UC-781 with polyethylene glycol 6000 and Gelucire 44/14. *Eur. J. Pharm. Sci. 10*, 311–322.

Dennis, A. B. (1988). Sustained Drug Release from Semi-solid Capsule Formulation. Ph. D. Thesis, The Welsh School of Pharmacy, Cardiff.

Dennis, A. B., Farr, S. J., Kellaway, I. W., Taylor, G., & Davidson, R. (1990). Evaluation of rapid release and sustained release Gelucire capsule formulations. *Int. J. Pharm. 65*, 85–100.

Doelker, C., Doelker, E., Buri, P., & Waginaire, L. (1986). The incorporation and in vitro release profiles of liquid deliquescent or unstable drugs with fusible excipients in hard geltin capsules. *Drug Dev. Ind. Pharm. 12*, 1553–1565.

Dordunoo, S. K., Ford, J. L., & Rubinstein, M. H. (1991). Preformulation studies on solid dispersions containing triameterene or temazepam in polyethylene glycols or Gelucire 44/14 for liquid filling of hard gelatin capsules. *Drug Dev. Ind. Pharm. 17*, 1685–1713.

Dordunoo, S. K., Ford, J. L., & Rubinstein, M. H. (1996). Solidification studies of polyethylene glycols, Gelucire 44/14 or their disper-

sions with triamterene or temazepam. *J. Pharm. Pharmacol. 48*, 782–789.

Dubois, J. L., & Ford. J. L. (1985). Similarities in the release rate of different drugs from PEG 6000 dispersions. *J. Pharm. Pharmacol. 37*, 494–495.

Eastman Chemical Company. (1998). TPGS NF, Properties and applications, Publication EFC-226A, Kingsport, TN.

Equisabel, A., San Vicente, A., Igartua, M., Hernandez, R. M., Gascon, A. R., Calvo, M. B., & Pedraz, J. L. (1996). Influence of melting point and hydrophilic/lipophilic balance on the release of salbutamol sulfate from lipid matrices. *ST.P. Pharma. 6*, 365–369.

Ficarra, R., Ficarra, P., Calabro, M., & Costantino, D. (1991). Quantitative high-performance liquid chromatographic determination in pharmaceutical formulations. *IL Farmaco 46*, 403–407.

Ford, J. L. (1980). The current status of solid dispersions. *Pharm. Acta Helv. 61*, 69–88.

Gattefossé, Product literature, Gattefossé. (1999). Pharmaceutical excipient for oral semi-solid formulation, Gelucire 44/14-Prompt release and enhanced bioavailability, PF 96327, Ist Edition.

Ginés, J. M., Veiga, M. D., Arias, M. J., & Rabasco, A. M. (1995). Elaboration and thermal study of interaction between cinnarizine and Gelucire 53/10 physical mixtures and solid dispersions. *Int. J. Pharm. 84*, 161–166.

Grimm, W. (1998). Extension of the International Conference on harmonization tripartite guidelines for stability testing of new drug substances and products to countries of climatic zones III and IV. *Drug Dev. Ind. Pharm. 24*, 404–409.

Hancock, B. C., & Zografi, G. (1997). Characterization and significance of the amorphous state in pharmaceutical systems. *J. Pharm. Sci. 86*, 1–12.

Henck, J.-O., Griesser, U. J., & Burger, A. (1997). Polymorphie von Arzneistoffen, *Pharm. Ind. 59*, 165–169.

Higuchi, T., & Connors, K. A. (1965). Phase solubility techniques. *Adv. Anal. Chem. Instrum. 4*, 117–212.

Howard, J. R., & Gould, P. L. (1987). Drug release from thermosetting fatty vehicles filled into hard gelatin capsules. *Drug dev. Ind. Pharm. 13*, 1030–1045.

Khan, K. A. (1975). The concept of dissolution efficiency. *J. Pharm. Pharmacol. 27*, 48–49.

Khoo, S. M., Porter, C. J. H., & Charman, W. N. (2000). The formulation of halofantrine as either non-solubilising PEG 6000 or solubilising lipid based solid dispersions: physical stability and absolute bioavailability assessment. *Int. J. Pharm. 205*, 65–78.

Laine, E., Auramo, A., & Kahela, A. (1988). On the structural behavior of triglycerides with time. *Int. J. Pharm. 43*, 241–247.

Lloyd, G. R., Craig, D. Q. M., & Smith, A. (1997). An investigation into the melting behavior of binary mixes and solid dispersions of paracetamol and PEG 4000. *J. Pharm. Sci. 86*, 991–996.

Martin, L., Wilson, C. G., Koosha, F., Tetley, L., Gray, A. I., Senel, S., Uchegbu, I. F. (2002). The release of model macromolecules may be controlled by the hydrophobicity of palmitoyl glycol chitosan hydrogels. *J. Control. Release 80*, 87–100.

Passerini, N., Perissutti, B., Moneghini, M., Voinovich, D., Albertini, B., Cavallari, C., & Rodriguez, L. (2002). Characterization of carbamazepine-Gelucire 50/13 microparticles prepared by a spray-congealing process using ultrasounds. *J. Pharm. Sci. 91*, 699–707.

Pinto, J. F., & Silverio, N. P. (2001). Assessment of the extrudability of three different mixtures of saturated polyglycolysed glycerides by determination of the "specific work of extrusion" and by capillary rheometry. *Pharm. Dev. Technol. 6*, 117–128.

Polli, J. E., Rekhi, G. S., Augsburger, L. L., & Shah, V. P. (1997). Methods to compare dissolution profiles and a rationale for wide dissolution specifications for metoprolol tablets. *J. Pharm. Sci. 86*, 690–700.

Rama Prasad, Y. V., Puthli, S. P., Eaimtrakarn, S., Ishida, M., Yoshikawa, Y., Shibata, N., & Takada, K. (2003). Enhanced intestinal absorption of vancomycin with labrasol and D-α- tocopheryl PEG 1000 succinate in rats. *Int. J. Pharm. 250*, 181–190.

Remunan, C., Bretal, M., Nunez, A., & Vila Jato, J. L. (1992a). Accelerated stability study of sustained release tablets prepared with Gelucire. *Int. J. Pharm. 80*, 151–159.

Remunan, C., Mrhar, A., Primozic, S., Karba, R., & Vila Jato, J. L. (1992b). Sustained nifedipine formulations: moment, modeling and simulation as pharmacokinetic analysis approach. *Drug Dev. Ind. Pharm. 18*, 187–202.

Roussin, P., & Laforet, J.-P. (1997). Investigating semi-solid formulations: physical characterization and stability study of Gelucire registered trade mark 44/14. *Fram. Vestn. 48*, 260–261.

Saers Sjökvist, E., & Craig, D. Q. M. (1992). An investigation into the mechanisms of dissolution of alkyl p- aminobenzoates from PEG solid dispersions. *Int. J. Pharm. 83*, 211–29.

Serajuddin, A. T. M. (1999). Solid dispersions of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J. Pharm. Sci. 88*, 1058–1066.

Serajuddin, A. T. M., Sheen, P. C., Mufson, D., Bernstein, D. F., & Augustine, M. A. (1988). Effect of vehicle amphiphillicity on the dissolution and bioavailability of a poorly water-soluble drug from solid dispersions. *J. Pharm. Sci. 77*, 414–417.

Smith, A., Lampard, J. F., Carruthers, K. M., & Regan, P. (1990). The filling of molten ibuprofen into hard gelatin capsules. *Int. J. Pharm. 59*, 115–119.

Sutananta, W., Craig, D. Q. M., & Newton, J. M. (1994a). An investigation into the effect of preparation conditions on the structure and mechanical properties of pharmaceutical glycerides bases. *Int. J. Pharm. 110*, 75–91.

Sutananta, W., Craig, D. Q. M., Newton, J. M. (1994b). The effects of aging on the thermal behavior and mechanical properties of pharmaceutical glycerides. *Int. J. Pharm. 111*, 51–62.

Sutananta, W., Craig, D. Q. M., & Newton, J. M. (1995). An evaluation of the mechanism of drug release from glyceride bases. *J. Pharm. Pharmacol. 47*, 182–187.

Sutananta, W., Craig, D. Q. M., & Newton, J. M. (1996). The use of dielectric analysis as a means of characterizing the effects of moisture uptake by pharmaceutical glyceride bases. *Int. J. Pharm. 132*, 1–8.

Thies, C., Dos santos, I. R., Richard, J., Vandevelde, V., Rolland, H., & Benoit, J. P. (2003). A supercritical fluid-based coating technology: 1. Process considerations. *J. Microencapsul. 20*, 87–96.

Van den Mooter, G., Augustijins, P., Blaton, N., & Kinget, R. (1998). Physicochemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K 30. *Int. J. Pharm. 164*, 67–80.

Wu, S. H., & Hopkins, W. K. (1999). Characteristics of D-α-tocopheryl PEG 1000 succinatae for applications as an absorption enhancer in drug delivery systems. *Pharm. Tech. 23*, 52–60

Yüksel, N., Karataş, A., Özkan, Y., Savaşer, A., Özkan, S. A., & Baykara, T. (2003). Enhanced bioavailability of piroxicam using Gelucire 44/14 and Labrasol: in vitro and in vivo evaluation. *Eur. J. Pharm. Biopharm. 56*, 453–459.