Turkish J. Pharm. Sci. 2 (2), 51-62, 2005

PHYSICOCHEMICAL CHARACTERIZATION AND DISSOLUTION PROPERTIES OF CINNARIZINE SOLID DISPERSIONS

Bahar Selen KALAVA, Müzeyyen DEMİREL*, Yasemin YAZAN

Anadolu University, Faculty of Pharmacy, Department of Pharmaceutical Technology, 26470 Eskişehir, TURKEY

Abstract

Bioavailability of a calcium antagonist cinnarizine, known to have a low aqueous solubility, is low or variable. Enhancement of the dissolution behavior of such a drug material can improve its oral bioavailability. For the improvement of the dissolution rate, solid dispersions were prepared by fusion method due to the complete dispersion ability of the active ingredient. Two different lipid carriers were used of which one has a gastric solubility and the other does not. The dispersions prepared were filled into cellulose hard capsules. In vitro dissolution rates of the formulations prepared were compared to pure cinnarizine and a commercially available tablet. Active material/lipid ratio was found to be effective on the dissolution rates. Dissolution rates of cinnarizine from the solid dispersions prepared using a lipid with gastric solubility were increased when compared to pure cinnarizine while sustained with the other lipid. As a conclusion of the study, it was determined that the dissolution rate of cinnarizine could be enhanced or sustained by using different carriers with different ratios.

***Keywords**: Cinnarizine, Solid Dispersion, Fusion Method, Dissolution Rate, In Vitro Dissolution*

Sinnarizin Katı Dispersiyonlarının Fizikokimyasal Karekteristikleri ve Çözünme Özellikleri

Sudaki çözünürlüğü düşük olarak bilinen kalsiyum antagonisti sinnarizinin biyoyararlanımı değişken veya düşüktür. Bu özellikteki bir ilaç materyalinin çözünme davranışının iyileştirilmesi, oral biyoyararlanımı geliştirebilir. Çözünme hızının arttırılması için, katı dispersiyonlar, etkin maddenin dispersiyon yeteneğinin tam olduğu eritme yöntemiyle hazırlanmıştır. Çalışmada gastrointestinal sıvıda çözünebilen ve çözünmeyen iki farklı lipit taşıyıcı kullanılmıştır. Hazırlanan dispersiyonlar sert selüloz kapsüllere doldurulmuştur. Formülasyonların in vitro çözünme hızları, saf sinnarizin ve bir piyasa tabletiyle karşılaştırılmıştır. Etkin madde / lipit oranının çözünme hızı üzerinde etkili olabileceği bulunmuştur. Saf sinnarizin ile hazırlanan katı dispersiyonların çözünme hızları karşılaştırıldığında, mide sıvısında çözünen lipit kullanıldığında özellik artarken, diğer lipitle geciktirilmiştir. Çalışmanın sonucu olarak, sinnarizin'in çözünme hızının farklı taşıyıcılar ve farklı oranlar kullanılarak, arttırılabileceği veya kontrol edilebileceği saptanmıştır.

***Anahtar Kelimeler**: Sinnarizin, Katı Dispersiyon, Eritme Yöntemi, Çözünme Hızı, İn vitro çözünme.*

* **Corresponding author:** Tel.:+90-222-335 05 80 ext. 3631/3656/3642;
Fax: +90-222-335 07 50.
e-mail: mdemirel@anadolu.edu.tr

INTRODUCTION

Cinnarizine is a calcium antagonist agent which, as a consequence of its scarce wettability and poor aqueous solubility, exhibits variable dissolution and low bioavailability after oral administration. Also, frequent dose administration is needed because of its short elimination half-life (3-6 hours) (1, 2).

Several methods including administration together with fatty foods, lipidic excipients, formation of salts and amorphous structures, decreasing particle size, formulating as emulsions and liposomes have been used to improve the dissolution rate and thus the oral bioavailability of drug materials with low aqueous solubility (3-6). With the solid dispersion technology, some portion of the active agent saturates the gastrointestinal fluid immediately while the remaining portion is later solubilized either as colloidal particles or very small lipid globules. This results in a higher dissolution and bioavailability compared to the conventional capsule and tablet forms where dissolution of active ingredient is limited with the particle size following dispersion in the biological fluids (4).

Considering limitations in the *in vivo* conditions of cinnarizine, enhancement of the dissolution behavior and control of the dissolution rate was aimed in this study. Solid binary systems of cinnarizine formulated at different drug/lipid ratios were characterized by IR spectroscopy, X-ray diffractometry and differential scanning calorimetry (DSC) and tested for dissolution rates. One of the lipids used is known to improve the dissolution pattern (Gelucire 44/14®) while the other has a potential of prolonging the dissolution rate (Compritol 888 ATO®).

EXPERIMENTAL

Materials

Cinnarizine was supplied by Nobel İlaç San.Tic.A.Ş., Turkey and tested for its specifications. The two lipids, Compritol 888 ATO® and Gelucire 44/14®, were obtained from Gattefosse, France. All solvents used were of analytical grade.

Preparation of solid systems

Since light affects the stability of cinnarizine, all procedures were carried out under light-protected conditions (7, 8).

The preparation method and the ratio of cinnarizine were kept constant for all formulations in order to investigate the effect of the lipid type and amount on the release profiles. One of the vehicles was lauryl macrogol-32 glycerides (Gelucire 44/14®) with no toxic activity and which is used to enhance the aqueous solubilities of active agents in semi-solid formulations (9). The other excipient was inert glyceryl behenate (Compritol 888 ATO®) known to release the active agent in a prolonged manner and which has very limited side effects even at high concentrations (10). Following the preliminary studies on the type of Gelucire and the different cinnarizine/lipid ratios for the two vehicles, 4 formulations were selected for further studies, considering the dissolution rate, content uniformity and unwanted physical appearance. Those formulations are given in Table 1.

Fusion method was used for the preparation of solid dispersion formulation (10). Preparation steps of solid dispersions are shown in Figure 1. Caution was taken not to exceed 70°C during the

heating process. Solid dispersions containing 25 mg of cinnarizine (equal to the amount in the commercial tablet) were manually filled into cellulose capsules of Number 0.

UV spectrophotometry

Since UV-spectrophotometer was used for the calculation of cinnarizine amount in capsule content and dissolution studies, this method was validated. pH 1.2 buffer was used as the solution medium for all studies (11).

Table 1. Solid dispersion formulation

Code	Cinnarizine (g)	Gelucire (g)	Compritol (g)	Active Agent-Lipid Ratio
F1	2	10	-	1:5
F2	5	5	-	1:1
F3	5	-	5	1:1
F4	5	-	2.5	1:0.5

For the determination of cinnarizine in the capsule, exact amount of one capsule content was carefully weighed, mixed with certain amount of pH 1.2 solution in the mortar and then the mixture was transferred into a volumetric flask. The mortar, was washed with portions of pH 1.2 solution and the mixture in the volumetric flask was completed to 50 mL with pH 1.2 solution. The mixtures of formulations F1 and F2 were shaken for 15 mins in ultrasonic bath and F3 and F4 for 15 mins using ultraturrax at 8000 rpm and each mixture was filtered through Whatman No 42. Cinnarizine in the solutions was quantified using UV-spectrophotometer at the wavelength of 252 nm. Each test was repeated 6 times.

IR spectroscopy

Infra red spectra were obtained using a FTIR-Mattson 1000 apparatus. KBr disks were used for pure cinnarizine, Compritol 888 ATO® and the solid systems prepared with Compritol 888 ATO®. Nujol was used for Gelucire 44/14® and the solid systems prepared with Gelucire 44/14®. All samples were scanned in the range of 400 and 4000 cm^{-1}.

Particle size distribution

Malvern Mastersizer Hydro 2000-S was used to determine the particle size distribution of cinnarizine.

X-ray diffractometry

X-ray diffraction patterns of each of the ingredients and all of the solid dispersions containing different proportions of cinnarizine in the lipid matrices were recorded using Rikagu X-ray diffractometer, over the 5-40° 2θ range at a scan rate of 2° min^{-1}. The X-ray source was Cu-Kα with a Ni filter (40 kV, 30 mA).

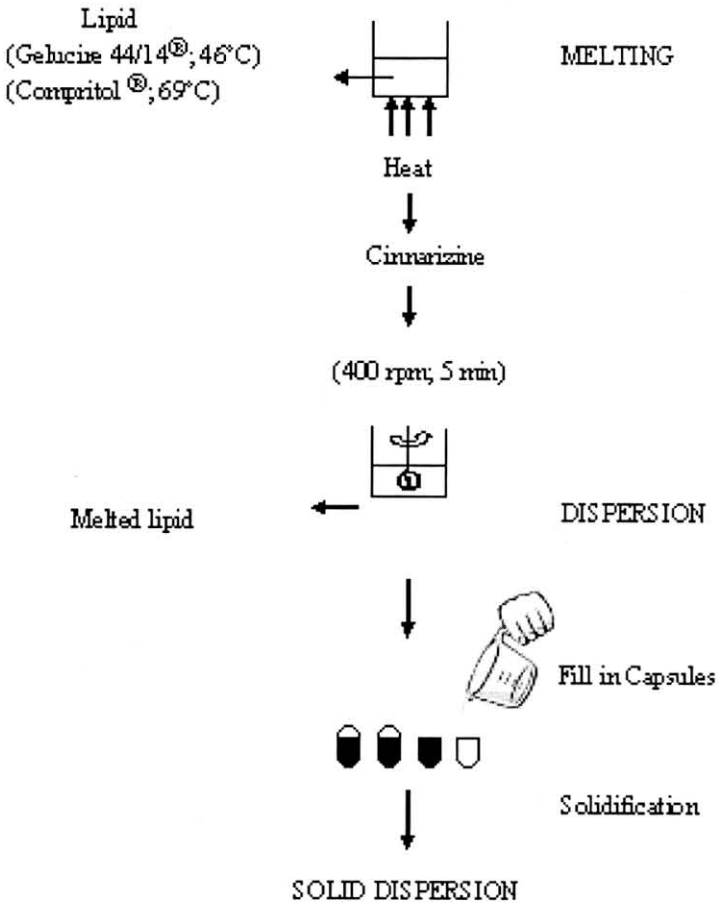

Figure 1. Preparation of cinnarizine solid dispersions by fusion method

Differential scanning calorimetry (DSC)

Shimadzu-DSC 60 differential scanning calorimeter was used to obtain the DSC curves representing the rates of heat uptake with respect to temperature. DSC curves were obtained for the pure ingredients and the solid systems prepared. Approximately 4 mg of sample was weighed in a standard open aluminum pan. An empty pan of the same type was utilized as the reference. The measurements were carried out under a nitrogen gas flow of 50 mL/min at a heating rate of 10°C/min.

IR spectra of the 4 formulations presented in Table 1, their X-ray patterns and DSC thermograms are given in Figure 2, Figure 3 and Figure 4, respectively.

Solubility measurements

Solubility of cinnarizine in pH 1.2 medium was determined using its saturated solution at room temperature and UV-spectrophotometer. The procedure was repeated 7 times and the mean value was taken. The solubilities in the two lipids were tested by DSC using the active agent/lipid ratios in the formulations.

Selection of filter material

To test the filter material which adsorbes the active substance in the minimum, solutions of cinnarizine with 4 different concentrations at pH 1.2 were prepared. 5 mL samples of the solutions were filtered through 3 different filter materials, namely cellulose acetate, cellulose nitrate, polyamide. Testing separately the 1st, 2nd, 3rd, 4th and 5th mLs of all filtrates, the amount of cinnarizine in each mL was calculated. The same procedure was repeated 3 times for each concentration value.

In vitro dissolution tests

The dissolution behaviour of cinnarizine alone and cinnarizine solid dispersions were determined using Apparatus No.1 defined in USP/NF XXIV. Experimental conditions were as follows: 500 mL pH 1.2 medium, 37±0.5°C temperature and 100 rpm stirring rate, assuring sink conditions. 5 mL samples were withdrawn from the dissolution medium at suitable time intervals, filtered through polyamide filter which was selected according to the adsorption tests, with a pore size of 0.2 μm. The same procedure was applied to the commercial tablet Sefal®. All samples contained 25 mg cinnarizine which is claimed for the commercial tablet. Dissolution profiles of pure cinnarizine, commercial tablet and the 4 formulations are presented in Figure 5.

RESULTS AND DISCUSSION

UV spectrum of cinnarizine showed a maximum wavelength at 252.0 nm which is in accordance with a previous study (12). The cinnarizine contents in the capsules of F1, F2, F3 and F4 solid dispersions are 24.59±0.47, 24.09±0.31, 21.25±0.45 and 26.14±0.76 (mg±SE), respectively.

Aromatic C-H bands at 3022 cm^{-1}, aliphatic C-H bands at 2957-2808 cm^{-1}, N^{+}-H bands at 2800-2500 cm^{-1} and C=C bands at 1600-1449 cm^{-1} were determined upon IR analysis of cinnarizine (Figure 2). The mean particle size of pure cinnarizine was found to be 33.75 μm. Since the material was used without further grinding or sieving, the heterogeneous particle size distribution was obtained as expected. Besides, due to the lipophilic character of cinnarizine, agglomeration may have occured upon contact with water.

Solubility of cinnarizine in pH 1.2 buffer solution was found to be 0.0058±0.44 (SE) g mL^{-1} (n=7). Since the peaks of both the active agent and the two lipids were detected on the thermograms (Figure 3), cinnarizine was determined not to dissolve in the two lipids at the ratios used.

Figure 2 demonstrates the IR spectra of the two lipids. C=O bands at 1750 cm^{-1} and C-O bands at 1115 cm^{-1} were seen in the spectrum of Gelucire®, while O-H bands at 3481 cm^{-1},

aliphatic C-H bands at 2956-2918 cm^{-1}, C=O bands at 1739 cm^{-1} and C-O bands at 1380-1191 cm^{-1} were seen in the IR spectrum of Compritol®.

Thermograms and X-ray diffraction patterns of Gelucire® and Compritol® are shown in Figure 3 and Figure 4, respectively.

Physicochemical characterization of solid dispersions

The physical state of cinnarizine in the Gelucire 44/14® and Compritol® lipids (solid dispersions) was studied by classical spectroscopic techniques (IR, DSC, X-ray diffraction).

The IR analyses of F3 and F4 showed the aromatic C-H bands at 3022 cm^{-1}, aliphatic C-H bands at 2957-2808 cm^{-1} and N^{+}-H bands at 2700-2500 cm^{-1} belonging to cinnarizine; and, C=O bands at 1739 cm^{-1} and C-O bands at 1140 cm^{-1} belonging to Compritol®. However, in the IR spectra of F1 and F2, there were no peaks of cinnarizine but only C=O bands at 1739 cm^{-1} and C-O bands at 1116 cm^{-1} which belongs to Gelucire 44/14®. Peak heights varied depending on the concentrations of the active ingredient and the lipids, in all spectra. Displacement due to new bond formation and loss of peaks in solid dispersion spectra are frequently seen in the literature (13) (Figure 2).

In the DSC analysis, pure cinnarizine exhibits a sharp melting event at 120.66°C with a fusion enthalpy of 102.08 J/g (Figure 3). Formulation of cinnarizine using lipid lipids has resulted in the loss of this melting peak for F1; replacement of a wide endothermic signal exhibiting reduced melting endotherm for F2, F3 and F4. Those weak, broad endotherms between 100°C and 116°C may be attributed to the melting of undissolved crystalline cinnarizine in the lipid. The presence of endothermic signals confirmed that some cinnarizine crystals still exist in the solid dispersions.

The loss of melting peak in F1 may be due to the low amount of cinnarizine in the sample since the ratio of active agent/lipid is 1:5. As reported in the literature, when the nominal drug content is 10%, no indication of crystalline drug can be detected in the thermogram (14). Cinnarizine probably consists of predominantly amorphous material, since no melting peaks were observed. Results of the dissolution studies which F1 has a higher dissolution rate then F2, also showed the same result. It is well known that the amorphous form of a drug generally has a higher apparent solubility than the crystalline counterpart, and in many cases also has a faster dissolution rate (15).

X-ray diffraction data of F2, F3 and F4 have lead to the fact that the active agent maintained its crystalline form within the lipid carriers (Figure 4). This means that the presence of Gelucire 44/14® and Compritol® at 1:1 and 1:0.5 active agent: lipid ratio in the solid dispersion has no influence on the physical state of cinnarizine. On the other hand, F1 solid dispersion has not shown sharp cristallinity. This indicates that cinnarizine is present in an amorphous form in this formulation, which is in accordance with a previous study (16). However, X-ray analysis is known to be invaluable when it is used alone in the evaluation of solid dispersions.

Generally, analytical investigations of solid dispersions agree in suggesting that the drug maintanes its crystalline form within the lipid. Solid dispersions tending to absorb a higher amount of moisture may lead to the induction of crystallization (17). The preparation conditions of the solid dispersions do not seem to induce polymorphism or amorphization of the drug, since their spectroscopic profiles are quite similar to the mere ingredients. The progressive disappearance of

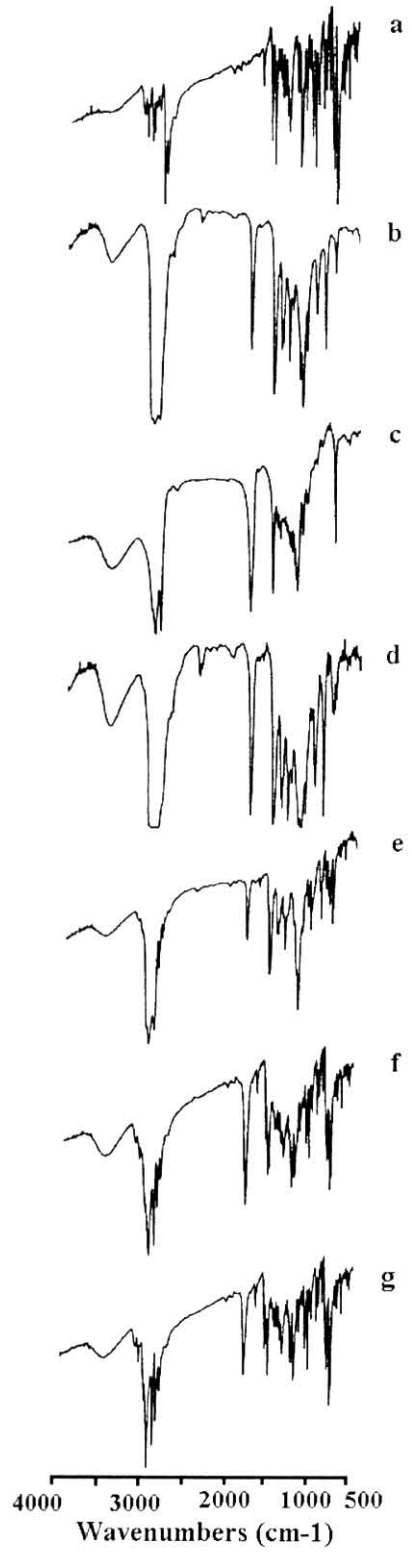

Figure 2. IR Spectra of **a:** Pure cinnarizine ; **b:** Gelucire® ; **c:** Compritol® ; **d:** F1 ; **e:** F2 ; **f:** F3; **g:** F4

drug IR, X-ray and DSC signals in the spectra of coevaporates is rather related to the increasing amount of the lipid, which exerts a "diluting" effect (the so-called "matricial effect") (18).

Dissolution studies

Type of the lipid and the cinnarizine/lipid ratio were found to affect the dissolution tests performed at pH 1.2, which appears to slow down by increasing the lipid amount (e.g. F3, F4). Rapid initial dissolution from formulations F1 and F2 was determined compared to pure active agent (Figure 5). The enhanced dissolution characteristics of solid dispersions can generally be attributed to one of the following mechanisms: eutectic formation, increased surface area of the drug due to the precipitation in the carrier, solid solution formation, improved wettability due to the intimate contact with a hydrophilic carrier, precipitation as a metastable crystalline form or a decrease in substance crystallinity (15). In this study, surface active character of the lipid leads to rapid dissolution of cinnarizine especially on or near the surface. Gelucire 44/14® may enhance the solubility of cinnarizine either by micellar solubilization or by reducing the activity coefficient of the drug by reduction in the hydrophobic interaction or by both processes. In addition, improvement in the wetting of the hydrophobic cinnarizine crystals may occur. It is found that the absence of crystalline drug material in solid dispersion is the prerequisite for a high dissolution rate, which is in accordance with a previous study (19).

Sustained release profile was obtained with F3 and F4 formulations when compared to pure cinnarizine (Figure 5). This is most probably due to the release prolongation potential of the lipid which is hydrophobic in character.

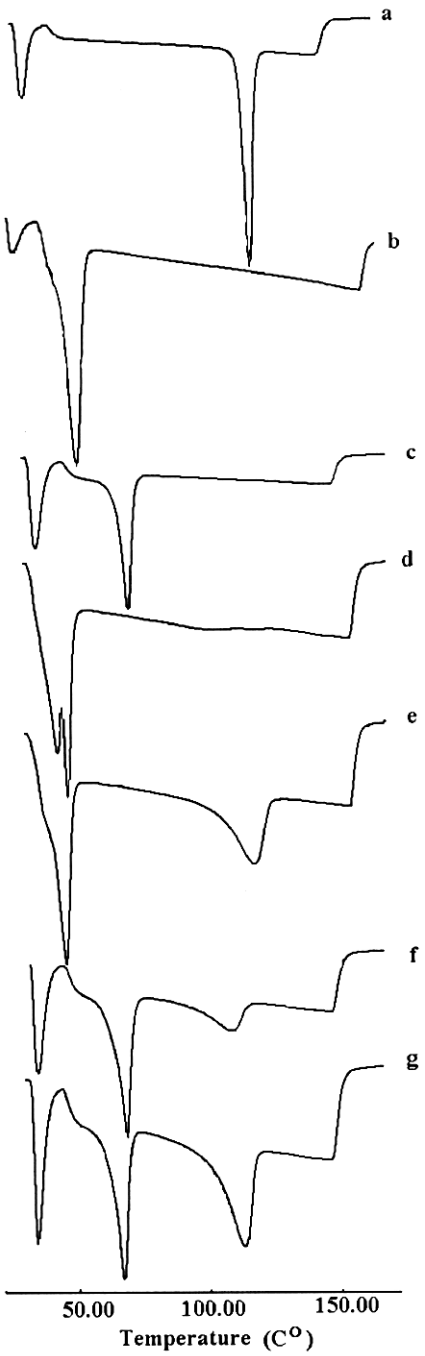

Figure 3. DSC termograms of **a:** Pure cinnarizine ; **b:** Gelucire® ; **c:** Compritol® ; **d:** F1 ; **e:** F2 ; **f:** F3; **g:** F4

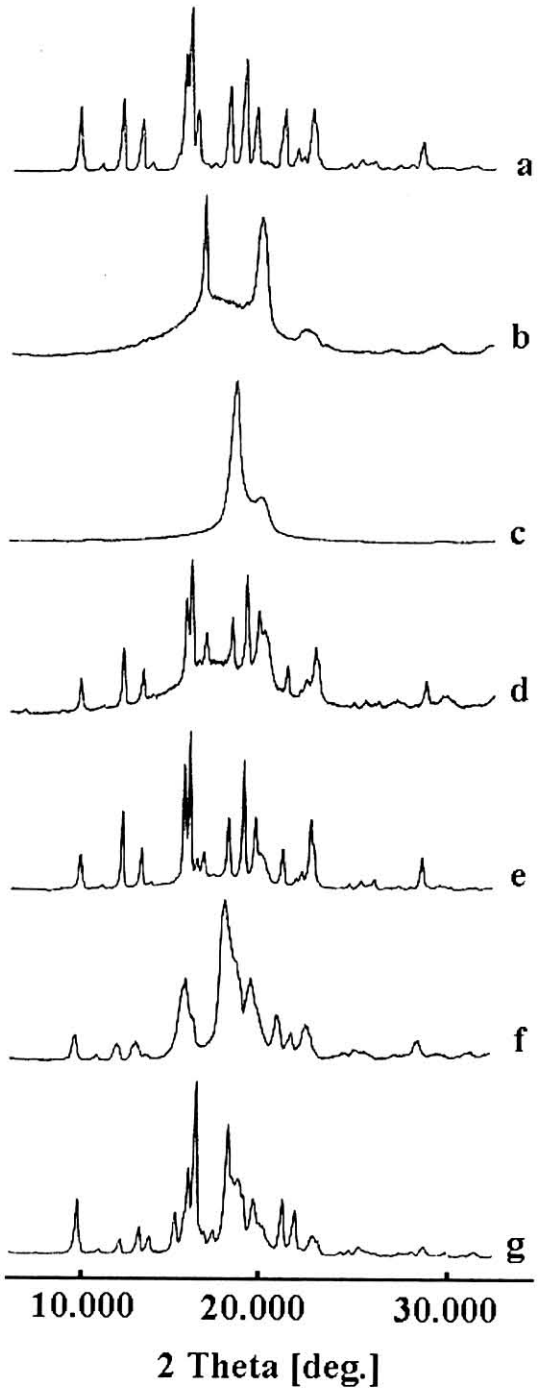

Figure 4. X-Ray diffraction patterns of: **a:** Pure cinnarizine ; **b:** Gelucire® ; **c:** Compritol® ; **d:** F1; **e:** F2 ; **f:** F3; **g:** F4

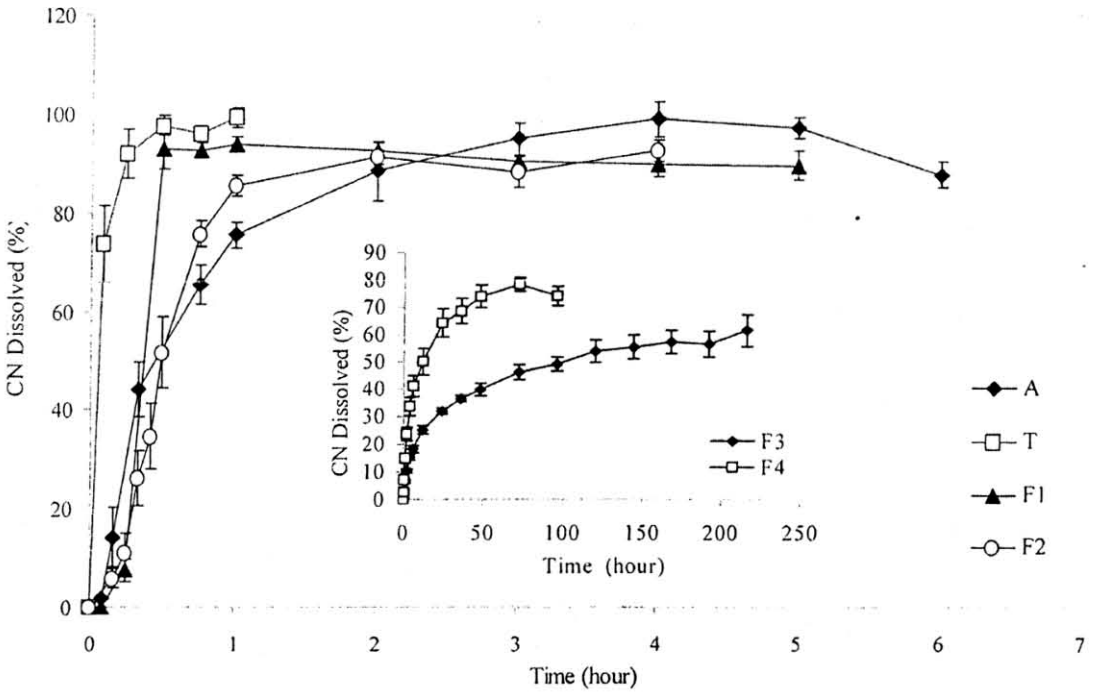

Figure 5. Dissolution profiles of cinnarizine from: **A:** pure cinnarizine; **T:** commercial tablet; **F1:** Cinnarizine - Gelucire 44/14® (1:5); **F2:** Cinnarizine - Gelucire 44/14® (1:1); **F3:** Cinnarizine - Compritol® (1:1); **F4:** Cinnarizine - Compritol® (1:0.5);

CONCLUSION

The results of our study seem to be promising in the sense of prolongation of the effects of cinnarizine looking at the dissolution profiles of F3 and F4. This may lead to the avoidance of frequent drug administration. The idea of increasing dissolution rate of cinnarizine may be realized by the use of lipids which are thermally stable and with surface active character.

REFERENCES

1. **Tokumura, T., Tsushima, Y., Tatsuishi, K., Kayano, M., Machida, Y., Nagai, T.,** "Enhancement of the oral bioavailability of cinnarizine in oleic acid in beagle dogs" J. Pharm. Sci. 76(4), 286-288, **1987.**

2. **Farre, A.J., Colombo, M., Fort, M., Gutierrez, B.,** "Differential effects of various Ca^{2+} antagonists" Gen. Pharmac. 22 (1), 177-181, **1991.**

3. **Otsuka, M., Onoe, M., Matsuda, Y., "**Hydroscopic stability and dissolution properties of spray-dried solid dispersions of furosemide with Eudragit" J. Pharm. Sci. 82(1), 32-38, **1993.**

4. **Serajuddin, A.T.M.,** Bioavailability enhancement of poorly water-soluble drugs by solid dispersion in surface active and self-emulsifying vehicles. In: Bull. Tech. Gattefossê 90, 43-50, **1997**.

5. **Mehta, S.C.,** "Issues and approaches for improving the solubility and bioavailability of poorly water soluble compounds," In: Bull. Tech. Gattefossê 91, 65-72, **1998.**

6. **Joshi, H.N., Tejwani, R.W., Davidovich, M., Sahasrabudhe, V.P., Jemal, M., Bathala, M.S., Varia, S.A., Serajuddin, Abu T.M.,** "Bioavailability enhancement of a poorly water-soluble drug by solid dispersions in polyethylene glycol-polysorbate 80 mixture" Int. J. Pharm. 269, 251-258. **2004.**

7. Martindale, The Extra Pharmacopoeia, 32th Edition, London Royal Pharmaceutical Society, England, 1999.

8. British Pharmacopoeia 1, The Stationery Office, England, 1998.

9. **Weyhers, H., Ehlers, S., Mehnert, W., Hahn, H., Müller, R.H.,** Proceeding of the 1st World Meeting on Pharmaceutics Biopharmaceutics Pharmaceutical Technology APGI/ APV, Budapest, 489, **1995**.

10. **Roussin, P., Laforét, J.P.,** Gelucire 44/14®: a high-performance system to enhance bioavailability of poorly water soluble drugs. In: Bull. Tech. Gattefossê 90,51-57, **1997**.

11. U. S. Pharmacopeia XXIV, NF 19, National Publishing, Philadelphia, p.2231-2232, 1999.

12. **Ling, S.,** "Determination of cinnarizine tablets by UV-spectrophotometry," Zhongguo Yiyuan Yaoxue Zazhi 13(4), 165-170, **1993.**

13. **Perng, C.Y., Kearney, A.S., Patel, K., Palepu, N.R., Zuber, G.,** "Investigation of formulation approaches to improve the dissolution of SB-210661 a poorly water soluble 5-lipoxygenase inhibitor" Int. J. Pharm. 176, 31-38. **1998.**

14. **Juppo, A.M., Boissier, C., Khoo, C.,** "Evaluation of solid dispersion particles prepared with SEDS" Int. J. Pharm. 250, 385-401. **2003.**

15. **Broman, E., Khoo, C., Taylor, L.S.,** "A comparison of alternative polymer excipients and processing methods for making solid dispersions of a poorly water soluble drug" Int. J. Pharm. 222, 139-151. **2001.**

16. **Van Nijlen, T., Brennan, K., Van den Mooter, G., Blaton, N., Kinget, R., Augustijn, P.,** "Improvement of the dissolution rate of artemisinin by means of supercritical fluid technology and solid dispersions" Int. J. Pharm. 254, 173-181. **2003.**

17. **Damian, F., Blaton, N., Kinget, R., Van den Mooter, G.,** "Physical stability of solid dispersions of the antiviral agent UC-781 with PEG 6000, Gelucire® 44/14 and PVP K30" Int. J. Pharm. 244, 87-98. **2002.**

18. **Pignatello, R., Ferro, M., De Guidi, G., Salem,, G., Vandelli, M.A., Guccione, S., Geppi, M., Forte, C., Puglisi, G.,** "Preparation, characterization and photosensitivity studies of solid dispersions of diflunisal and Eudragit RS100® and RL 100®" Int. J. Pharm. 218, 27-42. **2001.**

19. **Urbanetz, N.A., Lippold, B.C.,** "Solid dispersions of nimodipine and polyethylene glycol 2000: dissoluiton properties and physico-chemical characterisation" European Journal of Pharmaceutics and Biopharmaceutics 59, 107-118. **2005.**

received: 25.08.2004
accepted: 30.05.2005