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Enhanced Dissolution Rate of Tiaprofenic Acid Using Gelucire®44/14*

M. S. Saygılı, G. Uzunkaya, Y. Özsoy, A. Araman**

University of Istanbul, Faculty of Pharmacy,
Department of Pharmaceutical Technology, 34452-Beyazıt, Istanbul,
TURKEY

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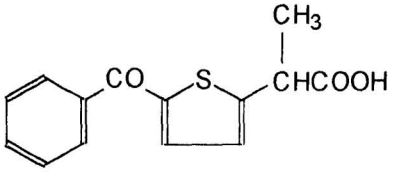
Summary

Tiaprofenic acid, a water insoluble drug, was dispersed in the melted Gelucire®44/14 at 1:1 ratio and the resulting thermosoftening solid dispersion was encapsulated into size 0 hard gelatin capsules. The release of tiaprofenic acid from capsules was evaluated by the dissolution test according to USP XXIII paddle method using distilled water and simulated gastric fluid as dissolution medium. In addition, the dissolution of hard gelatin capsules containing tiaprofenic acid dispersed in various PEGs with that of the pure drug was also investigated for comparison. The results showed that Gelucire® 44/14 was able to effect a remarkable increase in the dissolution rate of tiaprofenic acid.

Introduction

Tiaprofenic acid (TA), racemic (5-benzoyl-2-thienyl)-propionic acid (Fig. 1) is a 2-aryl propionic acid derivative nonsteroidal anti-inflammatory drug (1). TA is practically insoluble in water, freely soluble in acetone, in alcohol and in methylene chloride (2).

Fig. 1. Tiaprofenic acid



TA is used for the relief of pain and in rheumatic disorders such as osteoarthritis and rheumatoid arthritis. It is a potent inhibitor of prostaglandin synthetase enzymes which are known to be associated with inflammation and pain (3,4).

The formation of solid dispersions is an effective method of increasing the dissolution rate of poorly soluble drugs, and hence of improving their bioavailability (5-8). Solid dispersion is defined as the dispersion of one or more active ingredients in an inert carrier or matrix (9) and it has been reported that some of the problems associated with processing (e.g. pulverization, compression, etc.) of solid dispersions may be avoided by encapsulating the formulation in hard or soft gelatin capsules as a liquid melt (10).

The main formulation and manufacturing routes for preparing capsule formats of thermosoftening solid dispersions are well established (9,11). These formulations may be prepared using carriers with varying melting points and hydrophilic-lipophilic balance (HLB), selected according to the solubility characteristics of the drug and the required *in vitro* release profile (12).

Gelucire® 44/14 is a reversible heat meltable excipient and has proved to be of great interest in the manufacturing of semisolid formulations. It has a nominal melting point of 44°C and a HLB value of 14 (13). Gelucire®44/14 is commonly used as an excipient for immediate release dosage form that increases solubility of hydrophobic drugs and enhances bioavailability (14,15).

The purpose of the present study was to obtain an oral dosage form which has increased solubility using thermosoftening agent (Gelucire®44/14). Formation of the TA–Gelucire®44/14 thermosoftening solid dispersion was investigated employing X-ray powder diffraction, Infra-Red (IR) spectroscopic and Differential Scanning Calorimetry (DSC) analysis. In addition, the dissolution profile of the Gelucire®44/14-TA solid dispersion was compared with dissolution profiles of hard gelatin capsules containing TA dispersed in various PEGs (PEG 1500, 2000, 4000 and 6000) and that of the pure drug.

Experimental

Materials

Tiaprofenic acid was obtained from Hoechst Pharm. Comp.; Gelucire® 44/14 from Gattefossé; Polyethylene glycols (PEGs) from Merck; Hard gelatine capsules (size 0) from Capsugel and the other chemicals were all of analytical grade.

Methods

Preparation of capsules containing tiaprofenic acid:

Thermosoftening solid dispersions of TA with Gelucire®44/14, PEG 1500, PEG 2000, PEG 4000 and PEG 6000 were prepared using the fusion carrier method (16). Each vehicle was melted at a temperature approximately 2°C above its melting point and drug was dispersed using mixers at 8000 rpm (CAT X 620). The resulting dispersion was manually filled into the bottom halves of size 0 hard gelatine capsules and the upper halves of the shells were replaced. The fill weight of each capsule was made up 1 g, 500 mg of this amount was TA and the remaining amount was selected vehicle. To obtained uniformity of content, all of the Gelucire®44/14 in the unit package were melted before weighing and then the dispersion was prepared.

Physical characterization testing:

Physical characterization was carried out using several physical tests. X-ray powder diffraction, DSC and IR spectroscopic analysis were performed to determine the physicochemical properties of Gelucire®44/14, pure drug and the Gelucire®44/14–TA dispersion samples.

X- ray powder diffraction analysis:

X-ray diffraction patterns of samples were investigated using a wide angle X-ray diffractometer (Huber Corp. Diffraktionstechnik, Rimstig) with application of Ca-K a_1-ray.

IR spectroscopic analysis:

IR spectra of samples were determined over the scanning range 4000-800 cm^{-1} at a scan period of 14 min. using IR spectrophotometer (FTIR, Perkin Elmer 1600) from KBr pellets.

DSC analysis:

DSC analysis of samples was performed by placing them in aluminium pans of a Perkin-Elmer DSC calorimeter. 10°C/min of scanning speed was applied in the temperature range of 20-350°C.

Assay of tiaprofenic acid in the hard gelatine capsules:

For preparation of standard curve, 100 mg of TA was accurately weighed and dissolved in 100 mL of phosphate buffer (pH 7.4, 0.2 M). Distilled water and simulated gastric fluid were not suitable for the UV assay of TA because of the insolubility of the drug in these mediums (2, 17). Phosphate buffer has been used for this purpose. Using the stock solution, the solutions were prepared at 1-10 mcg/mL concentrations. Absorbances of the solutions were measured spectrophotometrically (Shimadzu UV-1601) at 316 nm. The standard curve was plotted and the equation for the standard curve of TA is given as follows:

$y= 16.0279x - 0.1854$ $r^2= 0.998$

(y= concentration (mcg/mL, x= absorbance, r^2= determination coefficient)

For assay of TA in the hard gelatine capsules, the content of one capsule was taken in 100 ml of volumetric flask and added 70 mL of phosphate buffer (pH 7.4). TA was extracted from this mixture with heating in ultrasound bath (37±0.5°C) and cooled at room temperature (25±1°C). Then, it was adjusted to 100 ML with buffer solution and filtered through membrane filter (S&S[593]). After suitable dilution, absorbances of the solutions were measured at 316 nm and the amounts of TA in the capsules were calculated using the equation of standard curve. Each experiment was done in 5 times and the average values were calculated. The used carriers did not interfere with the UV analysis.

Dissolution studies:

The release of TA dispersed in Gelucire®44/14 from prepared capsules was evaluated at 37±0.5°C by the dissolution test according to USP XXIII paddle method rotation speed of 100 rpm for 0 to 3 hours. 900 ml distilled water or simulated gastric fluid*(USP XXII) were used as dissolution medium. Samples (0.1 mL) were withdrawn at predetermined time intervals and the removed volume was replaced immediately with fresh dissolution medium. Volumes taken from the dissolution medium were diluted to 10 mL with phosphate buffer (pH 7.4). A blank solution has been prepared by diluting 0.1 ml dissolution medium to 10 ml with phosphate buffer (pH 7.4). TA content of each sample was assayed as above and the cumulative percentage of dissolved drug was calculated. Experimental points were the average of at least three replicates and standard deviations did not exceed %5 of the mean value.

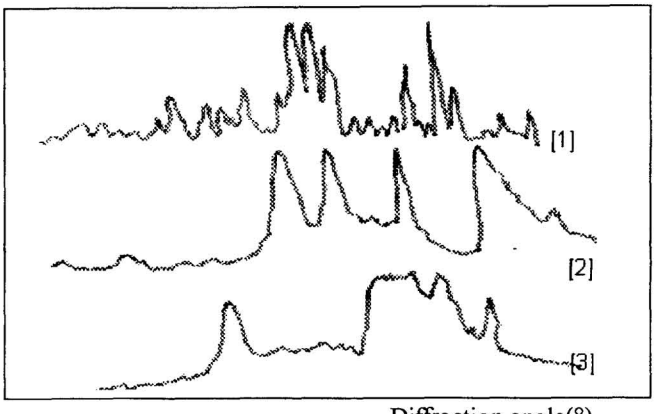
*Simulated Gastric Fluid: NaCl 2g, 1N HCl 80 ml, Distilled water ad. 1000 ml, pH 1.2, without pepsine.

Results and Discussion

X- ray powder diffraction analysis:

The X-ray powder diffraction pattern of pure drug exhibited its characteristic diffraction peaks at various diffraction angles indicating the presence of cristallinity, whereas dispersion with TA and Gelucire® 44/14 showed a diffraction spectrum to be decreased of characteristic diffraction peaks of TA (Fig.2). In case of solid dispersion, the absence and the reduction of major TA diffraction peaks indicates that an amorphous form existed in the solid dispersion.

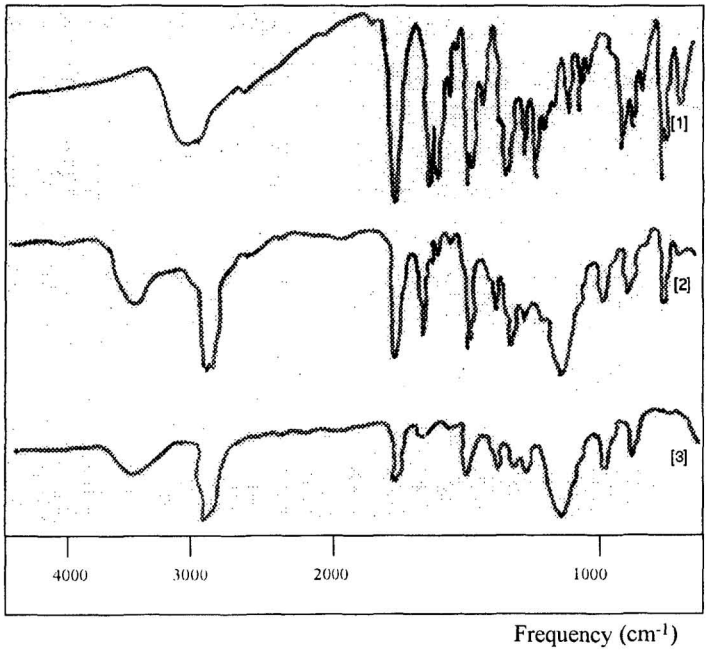
Fig. 2. Powder X-ray diffraction spectra of tiaprofenic acid [1], Gelucire®44/14 [2] and Gelucire®44/14 –TA dispersions [3]



IR spectroscopic analysis:

The IR spectroscopic analysis data of TA and Gelucire®44/14 alone and of solid dispersion are shown in Fig. 3. The bands of TA and Gelucire®44/14 were clearly visible in their spectra and are also discernible in the spectra of solid dispersion. The incorporation of TA into Gelucire®44/14 did not modify its peaks positions and trends. These results suggest that there was no chemical interaction between TA and Gelucire®44/14.

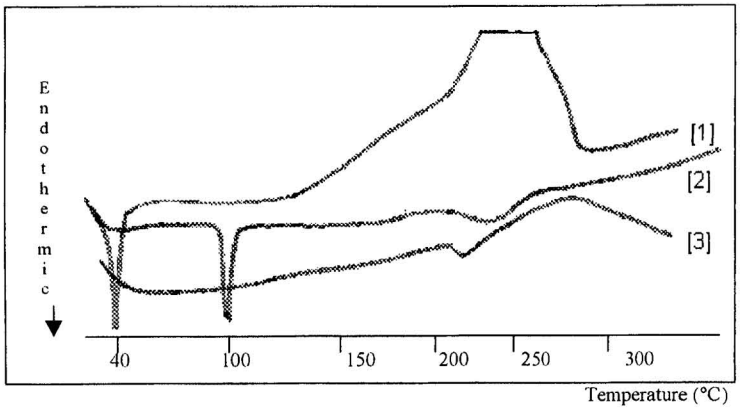
'g. 3. IR spectrum of tiaprofenic acid [1], Gelucire®44/14 –TA dispersions [2], Gelucire®44/14 [3]



DSC analysis:

As shown in Fig. 4, the thermographs of DSC show that Gelucire®44/14 – TA dispersion exhibits no peak, TA and Gelucire® 44/14 has a sharp peak at about 96°C and 44°C, corresponding to their melting point respectively. These data are in accordance with the postulate of almost amorphous state of the mixture and indicate that TA is penetrated through the solid dispersion and hence, a physical complexation is formed (12).

Fig. 4. DSC thermograms of Gelucire®44/14 [1], tiaprofenic acid [2], Gelucire®44/14 –TA dispersions [3]



Assay of tiaprofenic acid in the hard gelatine capsules:

The assay tests gave satisfactory results for all prepared capsules. TA amount of all the formulations was found between 98-102%. This results showed a good distribution of the drug in the prepared solid dispersions.

Dissolution studies:

Dissolution studies were performed for pure drug, its dispersion with Gelucire® 44/14 and PEGs. Data indicate that the dissolution rate of TA from Gelucire®44/14 is significantly higher than that of PEGs (Fig. 4 and 5) in both of the dissolution mediums. When distilled water was chosen as dissolution medium, the dissolved amount of TA from its dispersion with Gelucire®44/14 reached 100.02±1.07% at the end of 3 hours whereas the amount of drug liberated from the PEGs was 16.08±1.73%, 25.36± 0.15%, 25.30± 0.12% and 25.20± 0.10% for PEG 1500, 2000, 4000 and 6000, respectively. The dissolved amount of pure drug was also 66.33±5.09% after

3 hours. The formulations prepared with thermosoftening agents have showed similar results in the simulated gastric fluid. At the end of 3 hours, 98.04±1.02% of the drug was dissolved in the simulated gastric medium from Gelucire®44/14 dispersion, whereas the amount of drug liberated from the PEG 1500, PEG 2000, PEG 4000, PEG 6000 and pure drug were only 14.64±0.28%, 8.37±0.70%, 13.68±0.10%, 20.16±0.34% and 52.46±2.21%, respectively.

According to these release data, PEGs were shown delayed release for TA. This data are in accordance with the literature (14). There was no significant difference among the PEGs from the point of view release properties ($p>0.05$). The dissolved amount of TA from Gelucire® 44/14 solid dispersion increased approx. 70% and 30% than that of the PEGs and pure drug, respectively in the both of dissolution mediums.

Fig.5- *In vitro* release profile of tiaprofenic acid from the sodispersions prepared with Gelucire®44/14 and PEGs and pure drug (dissolution medium: distilled water)

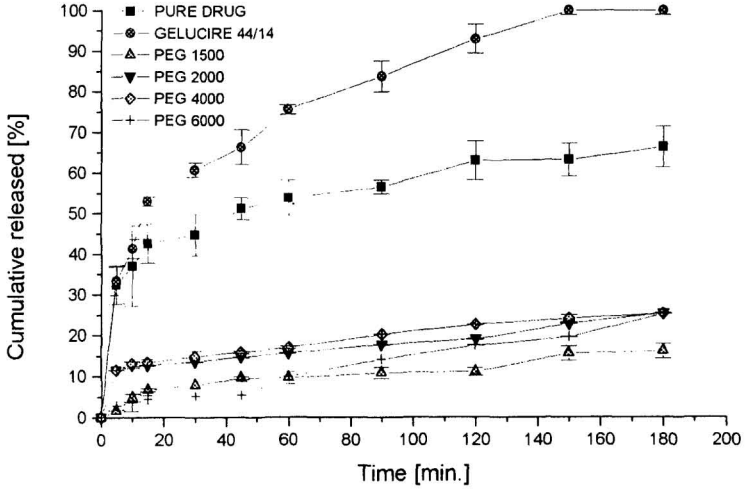
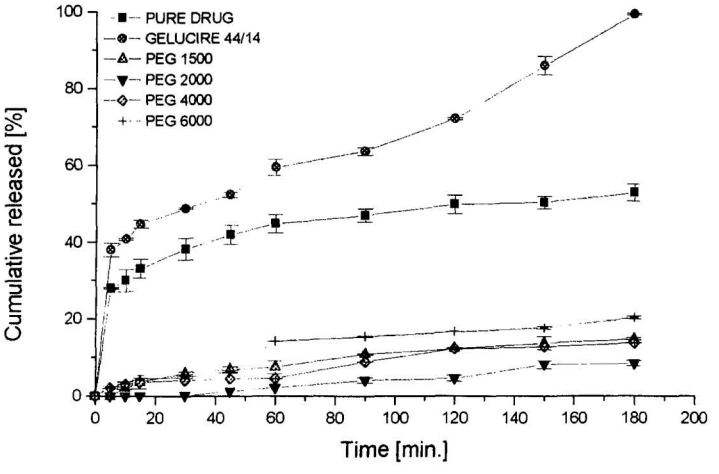


Fig.6- *In vitro* release profile of tiaprofenic acid from the solid dispersions prepared with Gelucire®44/14 and PEGs and pure drug (dissolution medium: simulated gastric fluid)



Conclusions

This study indicates that thermosoftening solid dispersion of TA with Gelucire® 44/14 improves the *in vitro* dissolution rates of TA. The increased dissolution may be attributed to increased wetting of the drug, because of the emulsifying properties of Gelucire® 44/14 (13). Gelucire® 44/14 was found to increase the dissolution of poorly soluble drugs due to its favourable water dispersible characteristics, as evident from their high HLB values represented by the second number in their designation. It has been reported that due to it's amphiphilic properties, Gelucire®44/14 forms an exceptionally stable and very fine (<1μm) emulsion when brought in contact with physiological fluids at 37°C (18). Gelucire® 44/14 rapidly disperses in the dissolution medium, independent of the pH value and it is commonly

used as an excipient for immediate release dosage form that increases solubility of hydrophobic drugs and enhances bioavailability (13). Due to the lack of surface activity of PEG 1500, 2000, 4000 and 6000, the dissolution of TA from these vehicles was incomplete whereas the dissolution of TA in water and simulated gastric fluid were complete with Gelucire® 44/14. The rates of dissolution of TA from capsules liquid filled with solid dispersions in PEG matrices were very low and the variation of dissolution from PEG matrices was only slightly. At the end of 180 minutes the released amount of TA was not higher than %20 from PEG matrices in both of the dissolution mediums.

In this study visual examination of the capsules following dissolution showed that after disintegration of the gelatin shell, the capsule contents remained solid and then dissolved in the dissolution medium by erosion. The dissolution of TA in the simulated gastric fluid and in distilled water from PEG 1500,2000,4000 and 6000 was incomplete (Figs 5 and 6); the released drug coated the surface of the solid as a hydrophobic layer, thereby retarding further dissolution. The drug dispersed only partially in the dissolution mediums.

The drug from Gelucire® 44/14 also dissolved or dispersed by erosion. However due to the amphiphilic property of this vehicle, the drug was emulsified in aqueous media and did not coat the surface of the solid fill material. Therefore the dissolution and dispersibility of the drug in simulated gastric fluid and distilled water, respectively, were complete (Figs 5 and 6).

The obtained data showed that Gelucire® 44/14 can be used as the release excipient to increase the release of TA in a hard gelatin capsule formulation.

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