*AAPS PharmSciTech, Vol. 12, No. 4, December 2011 (© 2011)*
DOI: 10.1208/s12249-011-9680-4

*Research Article*

# Ethylcellulose-Based Matrix-Type Microspheres: Influence of Plasticizer RATIO as Pore-Forming Agent

**C. Tuba Sengel-Turk,[1] Canan Hascicek,[1] and Nursin Gonul[1,2]**

*Received 8 April 2011; accepted 23 August 2011; published online 2 September 2011*

***Abstract.*** In this study, ethylcellulose (EC)-based microsphere formulations were prepared without and with triethyl citrate (TEC) content of 10% and 30% by water-in-oil emulsion-solvent evaporation technique. Diltiazem hydrochloride (DH) was chosen as a hydrophilic model drug and used at different drug/polymer ratios in the microspheres. The aim of the work was to evaluate the influence of plasticizer ratio on the drug release rate and physicochemical characteristics of EC-based matrix-type microspheres. The resulting microspheres were evaluated for encapsulation efficiency, particle size and size distribution, surface morphology, total pore volume, thermal characteristics, drug release rates, and release mechanism. Results indicated that the physicochemical properties of microspheres were strongly affected by the drug/polymer ratio investigated and the concentration of TEC used in the production technique. The surface morphology and pore volume of microspheres significantly varied based on the plasticizer content in the formulation. DH release rate from EC-based matrix-type microspheres can be controlled by varying the DH to polymer and plasticizer ratios. Glass transition temperature values tended to decrease in conjunction with increasing amounts of TEC. Consequently, the various characteristics of the EC microspheres could be modified based on the plasticized ratio of TEC.

**KEY WORDS:** diltiazem hydrochloride; ethylcellulose; microspheres; plasticizer; triethyl citrate.

## INTRODUCTION

Developing oral modified release systems for highly water-soluble drugs has always been a challenge to the pharmaceutical technologists (1–3). Microspheres are one of the multiparticulate dosage forms that have been prepared to modify or retard the drug release rate of the highly water-soluble drugs in pharmaceutical formulations. They represent a polymeric matrix system containing the drug in a state of uniform distribution throughout the matrix (4–6). Cellulose-based polymers such as ethylcellulose (EC) find wide application in the preparation of matrix-type microspheres of water-soluble drugs to control the dissolution rate of drugs from the dosage forms (7–9).

Various formulation and process parameters, such as type of organic solvent, drug/polymer ratio, emulsion stirring rate, and phase ratio of the emulsion system, can influence the physicochemical properties of matrix-type microspheres, especially the drug release rate, to a greater or lesser extent. In recent years, several attempts to modify the drug release rate have been investigated, such as the use of additives like various surfactants (5,10). One of the new popular approaches is the addition of a plasticizer having a higher affinity towards the dissolution media, which may enhance drug release by acting as a pore former in the matrix structure of the microparticles (11–14).

Plasticizers can be various polymeric materials and high-boiling liquids with low molecular weight, which should disperse as homogeneously as possible in the polymers to be modified. They are generally used to modify and improve the mechanical, thermal, and adhesive properties of a polymeric matrix structure in the microparticulate drug delivery systems. It is quite prevalent to incorporate plasticizers in the microsphere formulations to improve the flexibility or distensibility of the polymer chains, yield a non-disintegrating polymer matrix, and form a less porous network. This behavior occurs because the plasticizer agent can weaken the intermolecular forces between the polymer chains, increasing the free volume by reducing the number of active centers available for rigid polymer–polymer contracts. They can potentially reduce the resiliency of the polymer and increase the plasticity of the network when the plasticized structure undergoes the stress loadings during tension (15–18). Although plasticizers are used in various film-coating applications, spray-dried microspheres, beads, pellets, and microcapsule preparations (7,19–24), the development and application of plasticizer in a microsphere matrix system as a release modifier is a new area (11,13). Many compounds can act as a plasticizer, including phthalate and phosphate esters, fatty acids, sorbitol, citrate, and glycol derivatives. Among these plasticizers, long-chain esters like triethyl and tributyl citrates are generally used as plasticizers in the matrix

[1] Faculty of Pharmacy, Department of Pharmaceutical Technology, Ankara University, Tandogan 06100, Ankara, Turkey.
[2] To whom correspondence should be addressed. (e-mail: gonul@pharmacy.ankara.edu.tr)

structure. Water-soluble and water-insoluble citrate-type plasticizers show different influence on plasticization time, which results in different release rates of the drug (20,21,25). TEC is a commonly used hydrophilic plasticizer with non-toxic and non-irritant structure (23,24). The type and amount of plasticizer affects the drug diffusion rate through the matrix via structural changes. It acts as a channeling agent and creates channels through which the drug leaches out, increases the wetting of the hydrophobic barriers of the matrix, or modifies the barrier properties of the polymer (3,18,26). The degree of plasticization of a polymer depends to a large extent on the amount of plasticizer in the formulation and the interactions between the plasticizer and the polymer. Proper selection of the plasticizer amount in order to minimize the formation of pores on the surface of the microspheres is of great importance (27,28).

The objective of this study was to investigate the effect of one such modifier excipient, the plasticizer ratio, on the drug release rate and physicochemical properties of prepared microspheres. For this purpose, triethyl citrate (TEC), a well-known hydrophilic plasticizer, was used as a pore-forming agent to modify release of the drug from EC-based matrix-type microsphere formulations.

## MATERIALS AND METHODS

### Materials

DH (Nobel Pharmaceutical Co., Istanbul, Turkey), which is a highly water-soluble drug, was chosen as a model drug. Span 80 (Sigma Chemicals Co., St. Louis, MO, USA) was used as surfactant, which enhances the dispersibility of the polymer droplets. EC (Sigma Chemicals Co., St. Louis, MO, USA) was used as a matrix-forming agent and TEC (Morflex, Greensboro, NC, USA) was used as a plasticizer in this study. All other chemicals were of analytical or reagent grade and used without further purification.

### Preparation of EC Microspheres

EC microspheres were prepared by the water-in-oil (W/O) emulsion-solvent evaporation technique (10). EC was dissolved in acetone. The plasticizer, TEC, was added to this solution based on the solid dry weight of EC content (0%, 10%, and 30% (*w*/*w*)) and mixed for 30 min. Then, the weighted amount of DH was dispersed in this solution and stirred at a temperature of less than 20°C for 1 h. This mixture was poured rapidly into the liquid paraffin containing Span 80 as a surfactant at a 1.35% (*w*/*v*) ratio for the dispersing medium. The resulting emulsion was continuously agitated at room temperature using a three-blade propeller stirrer (Stir-Pak®, Cole-Parmer Instruments Co., USA) at 1,200 rpm for 5 h, and the acetone was removed completely by evaporation. The solidified microspheres were filtered and washed twice with 200 ml *n*-hexane. The prepared EC microspheres were dried under vacuum at room temperature overnight and then stored in a desiccator. In this work, the drug/polymer ratio (1:1, 1:2, 1:3, and 1:4) was varied, keeping the amount of polymer and the solvent volume constant but decreasing the amount of drug used in all formulations. The contents of the various EC microsphere formulations prepared along with formulation codes are summarized in Table I.

### Determination of Encapsulation Efficiency of Microspheres

To determine the DH content, accurately weighted portions from each bach of EC microspheres were dissolved in methanol, and this clear solution was analyzed for DH content by using a UV–visible spectrophotometer (Shimadzu UV-1,202 Visible, Kyoto, Japan) at the $\lambda_{max}$ value of 239 nm ($n$=6). The percent encapsulation efficiency of the EC microspheres was calculated as the ratio of amount of drug entrapped to the total amount of drug added initially (29).

### Determination of Particle Size and Size Distribution of Microspheres

The mean particle size and size distribution of the EC microspheres were determined by laser diffraction granulometry (Sympatec HELOS (H0728) particle size analyzer, Clausthal-Zellerfeld, Germany). About 0.5 mg of microspheres were dispersed in purified water in the sample dispersion unit and then analyzed. Each determination was carried out in triplicate.

### Scanning Electron Microscopy

The shape and surface morphology of the prepared EC microspheres were observed by a scanning electron microscope (SEM; Jeol JSM-840A, Japan). The dried microspheres were dusted onto double-sided tape on an aluminum stub. The stubs were then coated with gold under an argon atmosphere in a gold-coating unit (Polaran E 5,100) to a thickness of 400 Å. The microspheres were viewed at an accelerating voltage of 25 kV.

### Differential Scanning Calorimetry

Thermal analysis was performed on the pure drug, polymer, and drug-loaded microsphere formulations with and without TEC using a differential scanning calorimeter

**Table I.** Contents of the Ethylcellulose Microsphere Formulations Prepared with Different Plasticizer and Drug/Polymer Ratios

| | Code and quantity (g) | | | |
|---|---|---|---|---|
| | D11T0[a] | D12T0[a] | D13T0[a] | D14T0[a] |
| | D11T10[b] | D12T10[b] | D13T10[b] | D14T10[b] |
| Content | D11T30[c] | D12T30[c] | D13T30[c] | D14T30[c] |
| DH (g) | 3.6 | 1.8 | 1.2 | 0.9 |
| Ethylcellulose (g) | 3.6 | 3.6 | 3.6 | 3.6 |
| Span 80 (g) | 2.2 | 2.2 | 2.2 | 2.2 |
| Acetone (ml) | 60 | 60 | 60 | 60 |
| Liquid paraffin (ml) | 200 | 200 | 200 | 200 |
| Drug/polymer | 1:1 | 1:2 | 1:3 | 1:4 |

[a] Without TEC
[b] TEC, 10% (0.36 g)
[c] TEC, 30% (1.08 g)

(DSC; Netzsch Geratebau DSC 204, Germany). All the samples (≅5 mg) were heated in aluminum pans using air atmosphere. The analysis was performed with a heating range of 20–300°C and a rate of 5°C/min (30).

### Porosity Measurements of Microspheres

Total pore volume of the TEC-plasticized EC microspheres was measured by nitrogen adsorption using a porosimeter (Quantachrome Instruments, Autoscan-60, ON, Canada). An adequate quantity of microspheres was placed in the glass cells and outgassed with nitrogen at 25°C for 2 h before analysis. The sample and reference cells were immersed in liquid nitrogen at −196°C and adsorption isotherm was obtained from the volume of nitrogen ($cm^3/g$) adsorbed onto the surface of microspheres as a function of relative pressure. Total pore volume was calculated by the software program of the computer.

### *In Vitro* Drug Release Studies

*In vitro* release studies of the drug-loaded EC microsphere formulations were carried out according to the USP 30/NF 25 paddle method (Sotax AT 7 Smart) under sink conditions. Purified water at 37±0.5°C was used as dissolution medium according to the monograph of DH at USP 30/NF 25 (31). After suitable dilution, the absorbance values of the samples were determined at the $\lambda_{max}$ of 236 nm using UV–visible spectrophotometer (Shimadzu UV-1,202 Visible, Kyoto, Japan). By means of the calibration curve equation, the DH concentrations of the dissolution medium were calculated. The data obtained from the drug release studies were kinetically evaluated using SPSS 9.0 for Windows (SPSS, Chicago, IL). The *in vitro* experiments were carried out in triplicate.

### Statistical Analysis

The data obtained from the determination studies of encapsulation efficiency, particle size and size distribution, and release rate of DH-loaded EC microspheres were analyzed statistically using unpaired Student's *t* test. A 0.05 level of probability was taken as the level of significance. An analysis of variance (one-way ANOVA) followed by Tukey's post hoc test with the statistical software package SPSS 9.0 for Windows was also used.

## RESULTS AND DISCUSSION

### Preparation of Matrix-Type Microspheres

In this study, different DH-loaded matrix-type EC microsphere formulations were prepared by the W/O emulsion-solvent evaporation technique. This technique works best for highly dosed freely water-soluble drugs like DH to provide high drug loading and suitable particle size and size distribution. According to our previous studies, acetone and liquid paraffin have been used as disperse phase and dispersing medium, respectively, due to the appropriateness of the dielectric constants and the solubility characteristics of DH and EC (10,29). Microspheres were prepared with and without TEC at two different ratios (10–30%, *w*/*w*) to investigate the plasticization effect on the drug release rate and physicochemical characteristics of the prepared microspheres. When a plasticizer is incorporated into a polymeric material, it improves the workability and flexibility of the polymer by increasing the intermolecular separation of the polymer molecules (28). According to this approach, the addition of a suitable amount of a plasticizer as an additive to the microsphere formulations can modify the various physicochemical properties of the prepared formulations, especially the release rate of the incorporated drug.

### Characterization of EC Microspheres

The results of the encapsulation efficiency, particle size analysis and total pore volume are given in Table II. The encapsulation efficiencies of DH into the EC microspheres were found in a wide range for all the formulations (69.13–84.22%) and were affected neither by the variation in the plasticizer levels investigated ($p>0.05$) nor by the drug/polymer ratios studied ($p>0.05$). All of these results indicated that the W/O emulsion-solvent evaporation technique was a very suitable preparation method for encapsulation of hydrophilic drugs.

The data describing the mean particle size of the EC microspheres showed that the mean particle diameter was affected by both the drug/polymer ratio and the plasticizer ratio investigated ($p<0.05$) for all the formulations. As seen in Table II, the mean particle diameter of the microspheres increased with decreasing polymer ratio in the disperse phase based on the various levels of TEC for all the prepared formulations. This can be explained due to increasing the viscosity of the disperse phase by increasing the drug amount and reducing the polymer ratio; the diameter of the droplets in the emulsion system increases, which is mirrored in the increased mean diameter of the microspheres (10,29). The width of the size distribution of the microsphere formulations is indicated by Span value. All microsphere formulations produced had a wide range of particle size distribution with Span values of 0.750–1.140 (Table II). The higher Span value indicates a broad particle size distribution due to the higher viscosity difference between the disperse phase and the dispersing medium. Different microsphere formulations showed similar Span value.

In order to determine the microstructure of the prepared EC microspheres, total pore volume was measured using nitrogen adsorption porosimetry. From nitrogen adsorption isotherms, some basic structural information such as BET surface area, mean pore size, pore size distribution, and total pore volume can be obtained (25). As seen from Table II, there was no significant difference in total pore volume measurements between all the microsphere formulations based on the variation in the drug/polymer ratio investigated ($p>0.05$). However, the total pore volume of the EC microspheres was found to be affected by the different amounts of the plasticizer ($p<0.05$). The microsphere formulations prepared with 30% TEC had the greatest pore volume compared with those prepared with 10% TEC and without TEC. The minimum pore volume was obtained in the microspheres prepared with 10% TEC, emphasizing the effect of a certain amount of plasticizer on the surface characteristic of the EC microspheres.

**Table II.** The Physicochemical Properties of EC-Based Microsphere Formulations

| Code | Theoretical drug content[a] (*w/w* %) | Actual drug content[b] (*w/w* %) | Encapsulation efficiency (%) | Mean diameter[b] (μm) | Span | Total pore volume[b] ($cm^3/g$) |
|---|---|---|---|---|---|---|
| D11T0 | 50.00 | 42.11±1.47 | 84.22 | 1,003.79±1.41 | 0.932 | 0.25±0.01 |
| D12T0 | 33.33 | 24.66±1.73 | 73.99 | 563.55±1.38 | 0.813 | 0.27±0.08 |
| D13T0 | 25.00 | 19.30±0.97 | 77.20 | 544.01±1.39 | 0.930 | 0.28±0.06 |
| D14T0 | 20.00 | 14.75±1.07 | 73.75 | 511.14±1.24 | 1.051 | 0.32±0.04 |
| D11T10 | 50.00 | 41.98±0.83 | 83.95 | 865.20±1.34 | 0.750 | 0.06±0.04 |
| D12T10 | 33.33 | 24.54±1.27 | 73.64 | 604.38±1.37 | 0.784 | 0.09±0.06 |
| D13T10 | 25.00 | 18.91±1.15 | 75.65 | 599.61±1.34 | 1.025 | 0.08±0.09 |
| D14T10 | 20.00 | 14.67±1.82 | 73.73 | 538.23±1.36 | 1.132 | 0.10±0.03 |
| D11T30 | 50.00 | 34.57±0.86 | 69.13 | 870.14±1.34 | 1.140 | 0.62±0.07 |
| D12T30 | 33.33 | 23.42±1.37 | 70.27 | 706.72±1.44 | 1.007 | 0.68±0.05 |
| D13T30 | 25.00 | 17.71±1.63 | 70.85 | 606.70±1.29 | 0.848 | 0.66±0.06 |
| D14T30 | 20.00 | 14.38±1.42 | 71.88 | 594.81±1.41 | 0.912 | 0.63±0.02 |

[a] Theoretical drug content expressed as ratio between mass of drug and polymer used in the formulation
[b] The values indicate mean±standard deviation

The shape and surface characteristics of the different microsphere formulations that were prepared with various TEC ratios are illustrated in Fig. 1. SEM observations showed that all of the microspheres prepared were spherical in shape, and the morphological characteristics of the EC microsphere formulations were extensively affected by the plasticizer ratio investigated. As shown in Fig. 1a, the microsphere formulations prepared without TEC (D14T0) had a porous structure; however, the microsphere formulations prepared with 10% TEC (D14T10) had a smoother surface than that of the microspheres prepared without TEC (Fig. 1b). The D14T10-coded microsphere formulation exhibited a smooth, homogeneous and nonporous surface. This can be explained by the existence of 10% plasticizer content in the formulation. When plasticizer was not used in the formulations, a porous structure was produced on the surface of the microspheres. However, increasing the plasticizer percentage in the microsphere formulations (from 10% to 30%) increased the porous nature on the surface of the microspheres (Fig. 1c). The plasticizer effect reduced at levels higher than 10%. The surface of the microsphere containing 30% TEC (D14T30) showed greater porous structure due to the higher amount of plasticizer used. The difference between the surface characteristics of the microsphere formulations arose from the different percentages of TEC existing in these formulations. With an increasing amount of plasticizer, reduction in the intermolecular attractive forces between the polymer chains increases, due simply to the higher number of plasticizer molecules located between the macromolecules. Thus, the mobility of the polymer chains increases, resulting in the creation of a more porous membrane. A suitable amount of plasticizer acts by penetrating between the chains of the polymeric matrix structure, thereby reducing the interactions among the polymer chains at a certain stage and decreasing the porosity of the matrix formed. It has been concluded that the addition of the extra amount of plasticizer to the EC microsphere formulations causes changes in the surface morphology and allows more pores to be present on the surface of the microspheres. The selection of an appropriate amount of plasticizer improved the flexibility of the polymer chains and formed a less porous network (22,24). Estimation of the porous structure observed from the SEM micrographs shows good agreement with that given by the pore size measurements.

Plasticizers are used to improve the processability, flexibility and elasticity of the polymers. These compounds alter the thermal properties of the polymer by disrupting the intermolecular interactions of the polymer chains. Plasticization of a polymer will result in a decrease in glass transition temperature (Tg) of the polymeric material. Below this temperature, the polymer exists in a glassy state characterized by a substructure with minimal polymer chain movement. Above the Tg, the polymer is in a rubbery state, which is usually characterized by regions with increased polymer chain movement and polymer elasticity (17,18,27). Figure 2 shows DSC curves of the pure drug, raw polymer and the microsphere formulations, which were prepared at a 1:4 drug/polymer ratio with different TEC contents, respectively. A sharp endothermic peak corresponding to the melting of crystalline DH was found at 217.2°C (Fig. 2a) (30). The thermal transition of the raw polymer, EC, was seen at 143.7°C just in the first derivative of the curve, and this was attributed to the Tg of the polymer (Fig. 2b). This result is similar to the DSC curve of EC reported previously by some researchers (19,32,33). When the DSC thermogram of the D14T0-coded microsphere formulation was investigated (Fig. 2c), it was observed that DH affected the Tg of EC and functioned as a plasticizer for the EC microspheres formulated without TEC. DH lowered the Tg of EC from 143.7°C to 72.0°C. This result indicated that DH was very effective in lowering the Tg of the EC and had a significant plasticization effect on EC. Wu and McGinity (27) reported similar observations in ibuprofen-Eudragit RS 30D films. On the other hand, according to the DSC curves of the EC microsphere formulations containing different ratios of TEC (Fig. 2d, e), it was shown that the Tg of EC significantly changed with the amount of plasticizer used in the microsphere formulations. The Tg of EC in the microsphere D14T10-coded formulation was found as 63.1°C (Fig. 2d), while the Tg of EC in the microsphere formulation that was prepared with 30% TEC

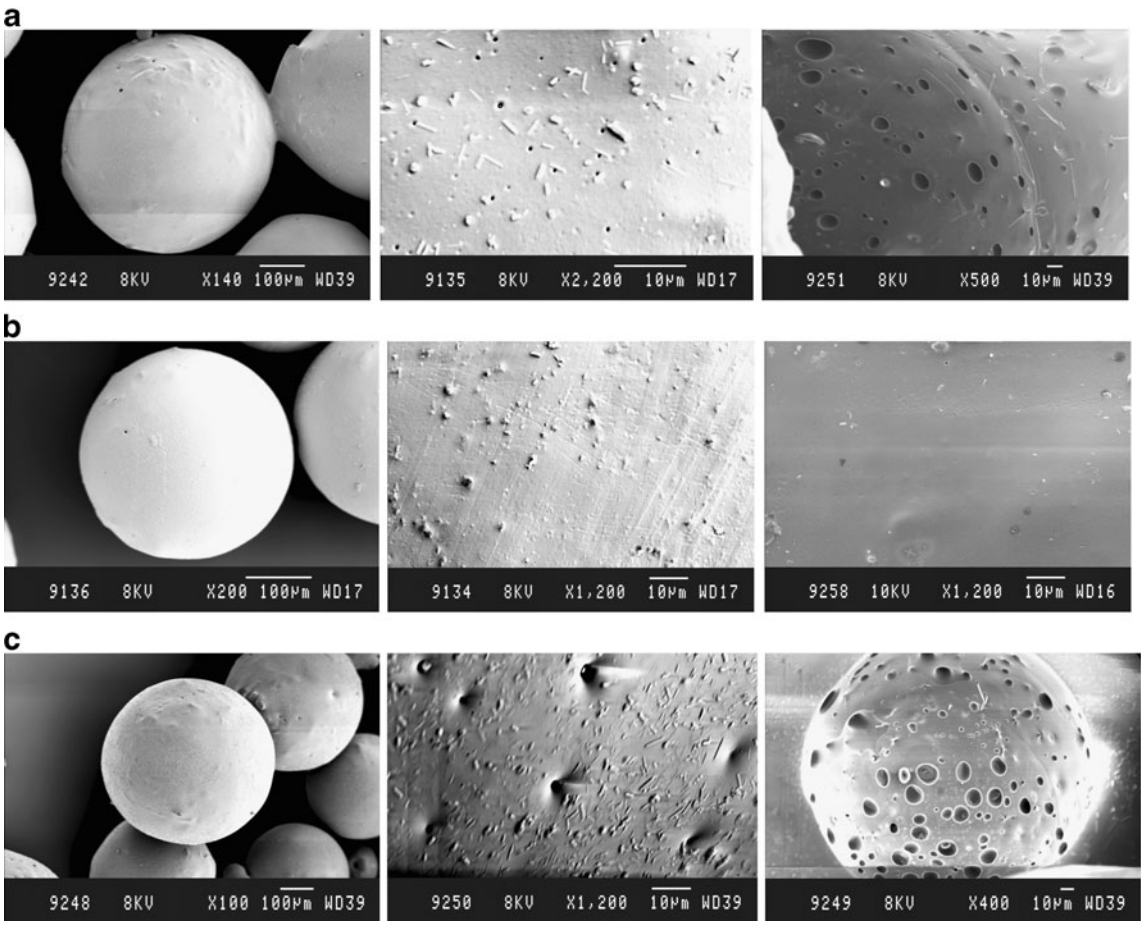


**Fig. 1.** Scanning electron micrographs of the surface and inner morphology of **a** D14T0-coded microspheres prepared without TEC, **b** D14T10-coded microspheres prepared with 10% TEC, and **c** D14T30-coded microspheres prepared with 30% TEC

(D14T30) was 54.6°C (Fig. 2e). This result indicated that the addition of increasing amounts of TEC decreases the Tg of the EC in the microsphere formulations. When the DSC curves of the EC microsphere formulations were investigated based on the physical status of DH in the microsphere structure, it was observed that DH showed a similar characteristic endothermic peak in all the formulations between 212.8°C and 214.9°C, indicating its melting point with varying intensity. The intensity of the DH peak in the microsphere formulations appeared to decrease. This may be due to a decrease in the degree of DH crystallinity in EC microsphere formulations at this drug/polymer ratio, indicating a mixture of both crystalline and amorphous forms of the drug in the microspheres.

The *in vitro* release profiles of the DH from EC microsphere formulations based on the investigated drug–polymer ratio are given in Figs. 3, 4, 5, and 6. All of the dissolution data were evaluated statistically by Student's *t* test and were found to be significantly different at each time point depending on the variation in the plasticizer level for all microsphere formulations ($p<0.05$). As the polymer concentration increased from 1:1 through 1:4, the drug release rate decreased based on the drug/polymer ratio (10). The release of drug from plasticized matrix-type microspheres is mainly dominated by the pore size and the interconnected channels on the polymeric matrix structure (20). It is apparent from the dissolution profiles that EC microspheres prepared with 30% TEC showed the fastest release behavior at each drug/polymer ratio. The increased release rate of DH from microspheres plasticized with 30% TEC is a result of the increased porosity of the matrix structure. A further increase in the TEC amount causes a reduction in the Tg of EC, which may have formed channels enhancing the release rate. However, the effect of plasticizer ratio on the drug release behavior of EC microspheres prepared with 1:3 drug/polymer ratio is different than other drug/polymer ratios for the initial 100 mins. An explanation for this behavior could be the presence of more drug crystals on the surface of these microsphere formulations (Fig. 5). When the dissolution profiles were observed with respect to the plasticizer ratio investigated, it was seen that a decrease from 30% to 10% in the plasticizer percentage resulted generally in a reduction in the drug release rate from the microspheres. This is because a plasticizer fraction of 10% leads to the formation of a nonporous matrix and decreases the permeability by decreasing the distance between the EC chains. It was shown that the release rate can be adjusted by the appropriate choice of the level of plasticizer. With a higher increase in plasticizer level, the diffusivity of the drug increases due to the higher mobility of the polymer chains that caused a more porous network (22). Further-

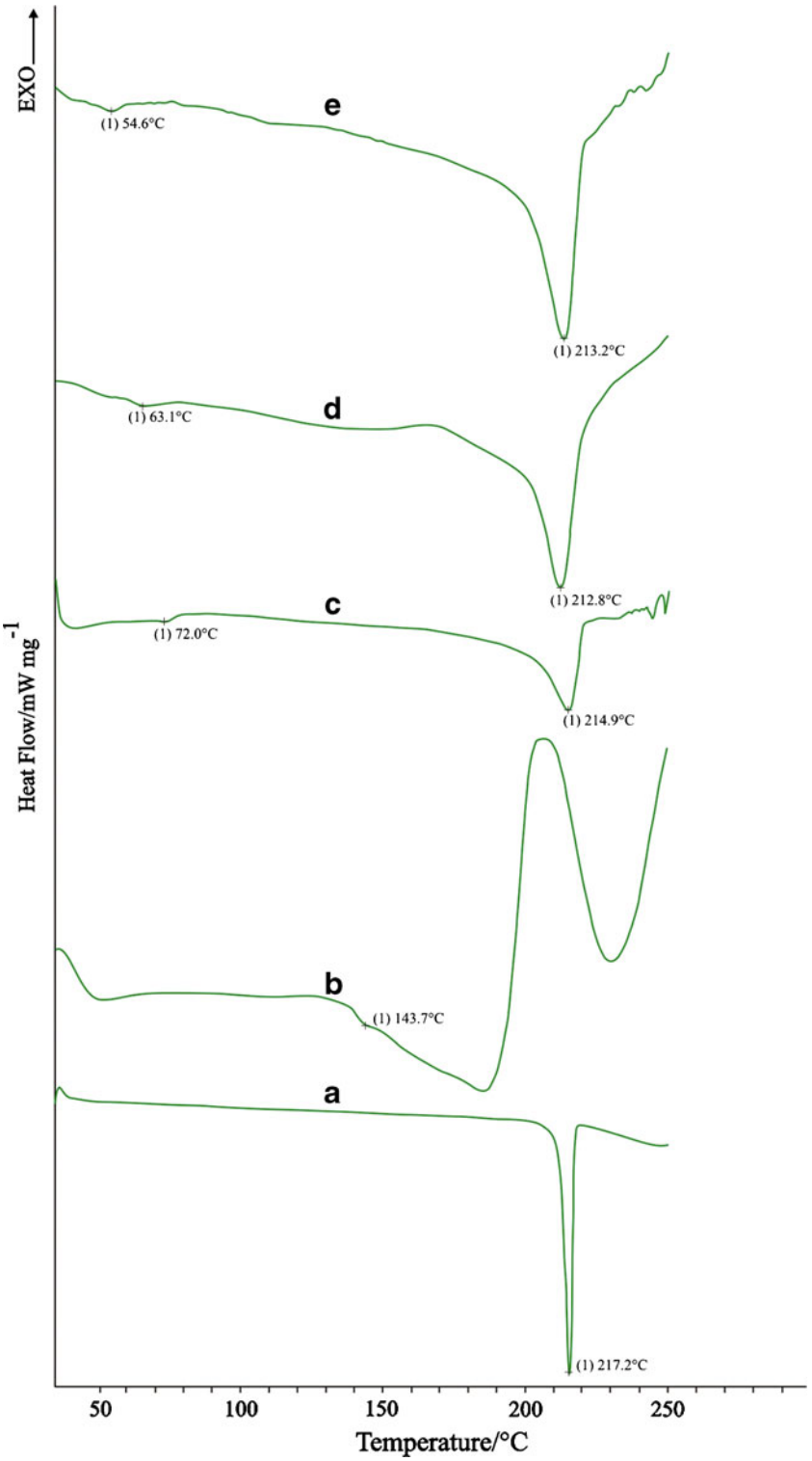


**Fig. 2.** DSC curves of the **a** DH, **b** EC, **c** D14T0-coded microspheres prepared without TEC, **d** D14T10-coded microspheres prepared with 10% TEC, and **e** D14T30-coded microspheres prepared with 30% TEC

more, it was seen that the dissolution rate of DH from EC microspheres prepared without TEC was faster than that of those plasticized with 10% TEC. The slowest release of DH from microspheres was observed with the formulations prepared incorporating 10% TEC at all drug/polymer ratios investigated, emphasizing the effect of the suitable amount of plasticizer on the drug release. When the effect of high water solubility of TEC on the drug release from EC microspheres was evaluated, it was considered that TEC leached into aqueous medium during drug release

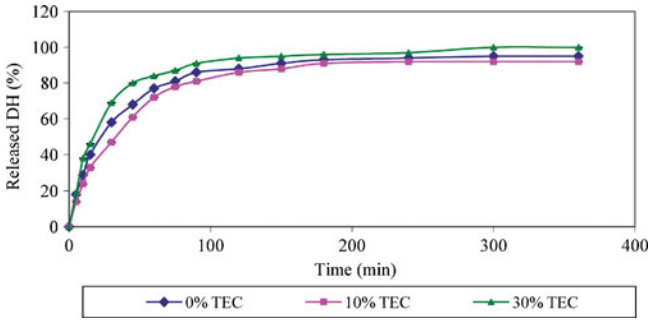


**Fig. 3.** Effect of plasticizer ratios on the drug release from DH-loaded EC microspheres prepared with 1:1 drug/polymer ratio

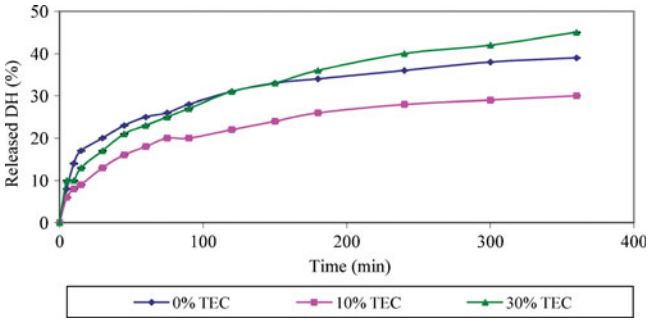


**Fig. 5.** Effect of plasticizer ratios on the drug release from DH-loaded EC microspheres prepared with 1:3 drug/polymer ratio

studies thereby generating visible pores. In this way, drug was released from those channels which were formed by TEC's migration. Dissolution results indicated that incorporation of a certain amount of plasticizer reduces the release rate significantly due to a decrease in the porosity of the matrix formed. When the quantity of plasticizer in the formulation was increased to a certain amount, it provided the formation of a better surface and limited the permeation of dissolution medium, thereby enabling control of the drug release rate by the barrier properties of the polymer. However, at the higher concentrations, the drug release rate increased because of the more porous nature of the polymeric matrix. Similar findings were reported previously by some other researchers (3,13). When the plasticizer level was investigated with respect to the drug/polymer ratio, it was observed that the effect of the plasticizer amount on the drug release rate increased with increasing polymer ratio and decreasing drug amount. The physical status of the drug in the polymeric matrix is another key factor influencing the drug release profile. The high crystallinity properties of DH in the matrix could lead to formation of a microchannel structure causing the drug to be released easily from the microspheres.

The *in vitro* drug release profiles were applied on various kinetic models in order to determine the mechanism of drug release. The release data obtained were evaluated by zero-order, first-order, and Higuchi kinetic models. For all of the formulations, considering the the highest determination coefficient, the best fit to Higuchi kinetic model was obtained, as seen in Table III. The drug release conformed to the Higuchi kinetic model, indicating that the drug release from EC microspheres was diffusion controlled and obtained from a matrix structure. The release mechanism of the EC microspheres plasticized using the water-soluble plasticizer, TEC, might have been pore diffusion. Diffusion through pores is considered to be more rapid than diffusion through membranes since the latter process involves the solubility of the drug in the polymer. Although EC is considered insoluble in water, it will swell in the presence of water. This is because of its hydrogen-bonding capability with water due to the polarity difference between the oxygen atom and the ethyl group of the polymer. When the various release modifiers are incorporated in the EC matrix, they create channels of different pore size, throough which the drug leaches out and they increase the wetting of the hydrophobic barriers of the matrix or modify the barrier properties of the membrane (26). Incorporation of a certain amount of plasticizer in the EC matrix may reduce the diffusion of water molecules inside the microsphere's matrix structure, thus reducing the formation of pores, resulting in slower release.

## CONCLUSIONS

This research investigated the influence of the plasticization effect of TEC that used as a pore-forming agent at various concentrations on the physicochemical characteristics of EC-based matrix-type microspheres. The choice of optimal amount of plasticizer has a decisive impact on the various physicochemical characteristics of the microspheres. The 10% concentration of TEC was the most

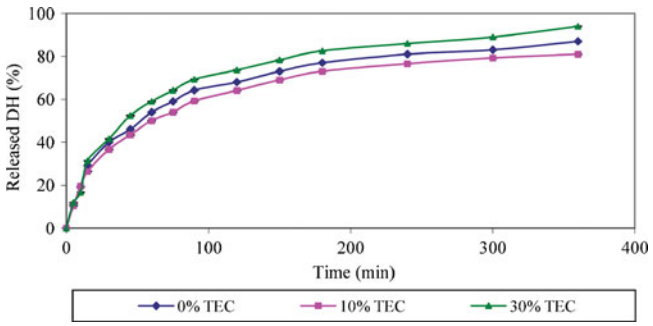


**Fig. 4.** Effect of plasticizer ratios on the drug release from DH-loaded EC microspheres prepared with 1:2 drug/polymer ratio

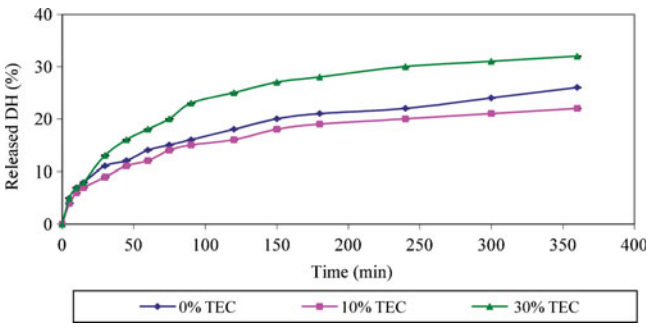


**Fig. 6.** Effect of plasticizer ratios on the drug release from DH-loaded EC microspheres prepared with 1:4 drug/polymer ratio

**Table III.** Release Kinetic Parameters of the Model Equations Applied to the *In Vitro* Release of DH from EC Microspheres

| | Kinetic model | | | | | |
|---|---|---|---|---|---|---|
| | Zero order | | First order | | Higuchi | |
| Formulation | $k_0$ (mg $h^{-1}$)[a] | $r^{2b}$ | $k_1$ ($h^{-1}$)[a] | $r^{2b}$ | $k$ ($h^{-1/2}$)[a] | $r^{2b}$ |
| D11T0 | 24.543 | 0.750 | 0.686 | 0.894 | 52.491 | 0.942 |
| D12T0 | 15.587 | 0.805 | 0.325 | 0.923 | 38.210 | 0.967 |
| D13T0 | 5.969 | 0.797 | 0.076 | 0.832 | 16.559 | 0.960 |
| D14T0 | 3.828 | 0.852 | 0.044 | 0.876 | 10.392 | 0.983 |
| D11T10 | 23.958 | 0.773 | 0.629 | 0.902 | 50.770 | 0.952 |
| D12T10 | 15.191 | 0.811 | 0.305 | 0.921 | 37.142 | 0.970 |
| D13T10 | 4.691 | 0.835 | 0.057 | 0.866 | 12.824 | 0.977 |
| D14T10 | 3.557 | 0.587 | 0.041 | 0.877 | 9.639 | 0.985 |
| D11T30 | 30.945 | 0.750 | 0.547 | 0.862 | 60.014 | 0.940 |
| D12T30 | 18.955 | 0.801 | 0.436 | 0.933 | 43.243 | 0.966 |
| D13T30 | 6.468 | 0.842 | 0.085 | 0.886 | 17.638 | 0.980 |
| D14T30 | 5.041 | 0.842 | 0.061 | 0.872 | 13.739 | 0.980 |

[a] Rate constant (unit)
[b] Determination coefficient

suitable amount for EC-based microspheres in order to significantly modify the surface morphology and release behavior of the microsphere formulations. As a results, TEC was a good plasticizer for EC-based matrix-type microspheres showing good compatibility and efficiency and the selection of the proper amount of plasticizer plays a very important role in achieving the desired physico-chemical properties of the matrix-type EC microspheres.

## ACKNOWLEDGMENTS

The authors would like to thank TUBITAK (The Scientific and Technical Research Council of Turkey) and the Management of Scientific Research Projects of Ankara University (project number: 2003.08.03.038) for their financial support of this study.

## REFERENCES

1. Abdul S, Chandewar AV, Jaiswal SB. A flexible technology for modified-release drugs: multiple-unit pellet system (MUPS). J Control Release. 2010;147:2–16.
2. Shamma RN, Basalious EB, Shoukri RA. Development and optimization of a multiple-unit controlled release formulation of a freely water soluble drug for once-daily administration. Int J Pharm. 2011;405:102–12.
3. Ye Z, Rombout P, Remon JP, Vervaet C, Mooter GV. Correlation between the permeability of metoprolol tartrate through plasticized isolated ethylcellulose/hydroxypropyl methylcellulose films and drug release from reservoir pellets. Eur J Pharm Biopharm. 2007;67:485–90.
4. Andreani L, Cercena R, Ramos BGZ, Soldi V. Development and characterization of wheat gluten microspheres for use in a controlled release system. Mat Sci and Eng C. 2009;29:524–31.
5. Mateovic T, Kriznar B, Bogataj M, Mrhar A. The influence of stirring rate on biopharmaceutical properties of Eudragit RS microspheres. J Microencapsul. 2002;19:29–36.
6. Nordstierna L, Abdalla AA, Nordin M, Nyden M. Comparison of release behaviour from microcapsules and microspheres. Progress in Org Coat. 2010;69:49–51.
7. Kangarlou S, Haririan I, Gholipour Y. Physico-mechanical analysis of freeethylcellulose films comprised with novel plasticizers of vitamin resources. Int J Pharm. 2008;356:153–66.
8. Lai HL, Pitt K, Craig DQM. Characterization of the thermal properties of ethylcellulose using differential scanning and quasi-isothermal calorimetric approaches. Int J Pharm. 2010;386:178–84.
9. Sogol K, Ismaeil H. Mechanical influence of static *versus* dynamic loadings on parametrical analysis of plasticized ethyl cellulose films. Int J Pharm. 2011;408:1–8.
10. Şengel CT, Hasçiçek C, Gönül N. Development and *in-vitro* evaluation of modified release tablets including ethylcellulose microspheres loaded with diltiazem hydrochloride. J Microencapsul. 2006;23:135–52.
11. Grattard N, Pernin M, Marty B, Roudaut G, Champion D, Meste ML. Study of release kinetics of small and high molecular weight substances dispersed into spray-dried ethylcellulose microspheres. J Control Release. 2002;84:125–35.
12. Hamedelniel EI, Bajdik J, Sovány T, Pintye-Hódi K. Delayed release matrix pellet preparation containing an alkalizing pore-former agent. Chem Eng Res Des. 2011. doi:10.1016/j.cherd.2010.12.003.
13. Schaefer MJ, Singh J. Effect of isopropyl myristic acid ester on the physical characteristics and *in vitro* release of etoposide from PLGA microspheres. AAPS PharmSciTech. 2000;1: Article 32.
14. Schilling SU, Shah NH, Malick AW, McGinity JW. Properties of melt extruded enteric matrix pellets. Eur J Pharm Biopharm. 2010;74:352–61.
15. Gutiérrez-Rocca J, McGinity JW. Influence of water soluble and insoluble plasticizers on the physical and mechanical properties of acrylic resin copolymers. Int J Pharm. 1994;103:293–301.
16. DiNunzio JC, Brough C, Miller DA, Williams III RO, McGinity JW. Applications of KinetiSol® dispersing for the production of plasticizer free amorphous solid dispersions. Eur J Pharm Sci. 2010;40:179–87.
17. Fadda HM, Khanna M, Santos JC, Osman D, Gaisford S, Basit AW. The use of dynamic mechnanical analysis (DMA) to evaluate plasticizztion of acrylic polymer films under simulated gastrointestinal conditions. Eur J Pharm Biopharm. 2010;76:493–7.
18. Vieira MGA, Silva MA, Santos LO, Beppu MM. Natural-based plasticizers and biopolymer films: a review. Eur Polym J. 2011;47:254–63.
19. Kojima M, Nakagami H. Development of controlled release matrix pellets by annealing with micronized water-insoluble or enteric polymers. J Control Release. 2002;82:335–43.
20. Lin WJ, Lee HK, Wang DM. The influence of plasticizers on the release of theophylline from microporous-controlled tablets. J Control Release. 2004;99:415–21.
21. Meier MM, Kanis LA, Soldi V. Characterization and drug-permeation profiles of microporous and dense cellulose acetate membranes: influence of plasticizer and pore forming agent. Int J Pharm. 2004;278:99–110.
22. Siepmann J, Lecomte F, Bodmeir R. Diffusion-controlled drug delivery systems: calculation of the required composition to achieve desired release profiles. J Control Release. 1999;60:379–89.
23. Tarvainen M, Sutinen R, Peltonen S, Mikkonen H, Maunus J, Vähä-Heikkilä K, *et al*. Enhanced film-forming properties for ethylcellulose and starch acetate using *n*-alkenyl succinic anhydrides as novel plasticizers. Eur J Pharm Sci. 2003;19:363–71.
24. Yang QW, Flament MP, Siepmann F, Busignies V, Leclerc B, Herry C, *et al*. Curing of aqueous polymeric film coatings: importance of the coating level and type of plasticizer. Eur J Pharm Biopharm. 2010;74:362–70.
25. Sant S, Nadeau V, Hildgen P. Effect of porosity on the release kinetics of propafenone-loaded PEG-g-PLA nanoparticles. J Control Release. 2005;107:203–14.
26. Emeje MO, Kunle OO, Ofoefule SI. Compaction characteristics of ethylcellulose in the presence of some channeling agents: technical note. AAPS PharmSciTech. 2006;7:Article 58.

27. Wu C, McGinity JW. Influence of ibuprofen as a solid-state plasticizer in Eudragit RS 30 D on the physicochemical properties of coated beads. AAPS PharmSciTech. 2001;2: Article 24.
28. Zhu Y, Shah NH, Malick AW, Infeld MH, McGinity JW. Solid-state plasticization of an acrylic polymer with chlorpheniramine maleate and triethylcitrate. Int J Pharm. 2002;241:301–10.
29. Şengel-Türk CT, Hasçiçek C, Gönül N. Microspheres-based once-daily modified release matrix tablets for oral administration in angina pectoris. J Microencapsul. 2008;25:257–66.
30. Türk CT, Hasçiçek C, Gönül N. Evaluation of drug-polymer interaction in polymeric microspheres containing diltiazem hydrochloride. J Therm Anal Cal. 2009;95:865–9.
31. USP 30/NF 25. Diltiazem hydrochloride. In: United States of Pharmacopoeia 30/National Formula 25. Rockville, USA: 2007. p. 1952–6.
32. Chow AHL, Ho SSS, Tong HHY, Ma HHM. Parameters affecting in-liquid drying microencapsulation and release rate of cefaclor. Int J Pharm. 1998;172:113–25.
33. Oh E, Luner PE. Surface free energy of ethylcellulose films and the influence of plasticizers. Int J Pharm. 1999;188:203–19.