

MICROPELLETISATION OF THEOPHYLLINE BY A SPRAY DRYING PROCESS AND THE EFFECT OF DIFFERENT COATING POLYMERS

TEOFİLİN İÇEREN MİKROPELLETLERİN PÜSKÜRTEREK KURUTMA YÖNTEMİ İLE HAZIRLANMASI VE DEĞİŞİK KAPLAMA POLİMERLERİNİN ETKİLERİ

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*In this study, micropelletisation of theophylline drug particles was carried out by a spray drying technique using an aqueous system. Comparison was made between the use of various polymers. Hydroxypropylmethylcellulose (HPMC), methylcellulose (MC), sodium carboxymethylcellulose (NaCMC) and Eudragit L 30 D were the polymers, which were studied to evaluate their spray coating properties. The results showed that drug release from the coated products was dependent on both the hydrophilicity of the polymer and the effect of the plasticizer. NaCMC, which is more hydrophilic, gelled faster and retarded the drug release more effectively. Eudragit L 30 D, with the effect of the plasticizer and the spheronizer in pH 7.4, also retarded the release. Spray coating with other polymers with or without plasticizer was unsuccessful. With the polymers, NaCMC and Eudragit L 30 D sustained drug delivery were evaluated.*

*Bu çalışmada, etken madde olarak kullanılan teofilinin sulu çözeltilerinden hareketle, püskürterek kurutma tekniği ile mikropelletizasyonu yapılmıştır. Hidroksipropilmetilselüloz (HPMC), metilselüloz (MC), sodyumkarboksümetilselüloz (NaCMC) polimerleri kullanılmış ve bunların spray kaplama özellikleri karşılaştırılmıştır. Sonuçlar, kaplanmış üründen etken madde çıkışının hem polimerin hidrofilitesine, hem de plastizer etkisine bağlı olduğunu göstermiştir. Daha hidrofilik olan NaCMC, daha hızlı jelleşerek, etken madde çıkışını daha etkin bir biçimde geciktirmiştir. Eudragit L 30 D de plastizer ve küreselleştirici ajan etkisi ile pH 7.4'de yine etken madde çıkışını geciktirmektedir. Diğer polimerlerle, plastizer kullanarak veya plastizer kullanmadan yapılan püskürterek kaplama başarısız bulunmuştur. NaCMC ve Eudragit L 30 D ile geciktirilmiş etki elde edilmiştir.*

**Keywords :** Spray drying; Theophylline; Polymer coating; Sustained release; Micropelletisation

**Anahtar kelimeler :** Püskürterek kurutma; Teofilin; Polimer kaplama; Sürekli etki; Mikropelletizasyon

## Introduction

Solid particles can be prepared directly from liquid droplets during spray drying(1,5,10). There has been a renewed interest in the use of spray drying to coat drugs with polymers to produce dust free controlled release products(6). The advantage of using this technique over other coating methods is that it is a one-step process applicable to heat sensitive and sterile materials(2). There are also a number of papers on the use of spray drying techniques involving an organic solvent base(1,3). The purpose of this study was to utilise spray drying to coat theophylline particles with an aqueous polymeric solution.

Coating of drug pellets with a non-soluble barrier membrane offers a reliable method of regulating the drug release(4,12). The coating can be varied in nature and thickness to give the desired release profile. Drug release from

the coated pellets occurs via diffusion of dissolved molecules through the continuous phase and plasticizer channels of the barrier membrane(7,8,12) and aqueous filled pores created by dissolution of soluble components incorporated into the coat(9).

Theophylline has been shown to be well absorbed throughout the gastrointestinal tract(12). This together with its narrow therapeutic index makes it suitable for sustained drug delivery.

This study aimed the development and invitro evaluation of a sustained release preparation of theophylline by spray drying process.

## Materials

The drug used was anhydrous theophylline (Siegfried). Coating polymers examined were hydroxypropy-

\* Correspondence

Imethylcellulose (HPMC; 4000 mPa.s; Fluka), sodium carboxymethylcellulose (NaCMC; Fluka), methylcellulose (MC; low viscosity; Fluka), Eudragit L 30 D (Röhm Pharma). Triethylcitrate and citric acid monohydrate (Merck) and polyethylen glycol 6000 (PEG 6000; Degussa) were the plasticizers and Aerosil 200 (Degussa) was the spheronizer used.

### Methods

The polymer was first hydrated in about 500 ml of distilled water and then the required plasticizer and the drug were added to the solution.

### Spray drying technique

The feed was continuously stirred while being spray dried (Büchi 190) using a pneumatic nozzle and the product was collected in a cyclone separator. The flow of feed was concurrent with the direction of the inlet drying air. The operating conditions adopted after preliminary experiments were:

|                        |  |
|------------------------|--|
| Inlet air temperature  | : 140±2°C                              |
| Outlet air temperature | : 70±2°C                               |
| Feed spray rate        | : 10±0.5 ml.min <sup>-1</sup>          |
| Aspiration rate        | : 15 m <sup>3</sup> .min <sup>-1</sup> |
| Atomizing air pressure | : 600 mmHg                             |

### Dissolution studies

The dissolution studies were assayed in the formulations which were coated successfully in the preliminary experiments (F-6, F-7). The release rate of theophylline from the spray dried products was determined using a dissolution apparatus (Method 1, USP XXII). The basket was rotated at 50 rpm. The dissolution medium was 900 ml of

1- pH 1.2 hydrochloric acid buffer

2- pH 7.4 phosphate buffer maintained at 37±0.5°C.

At specified time intervals over a period of 8 hours, 4 ml of samples were collected. The samples were then assayed spectrophotometrically at 270 nm (for pH 1.2 hydrochloric acid buffer) and 275 nm (for pH 7.4 phosphate buffer). At least three replicates were

Table 1. Formulations that were prepared by spray coating process (values are given in %)

| Formulations | Theophyllin | Polymer                  | Plasticizer  | Aerosil 200 | Distilled water |
|--------------|-------------|--------------------------|--|-------------|-----------------|
| F-1          | 2           | HPMC<br>0.6              | *Citric acid monohydrate<br>+<br>triethylcitrate<br>0.18 | -           | to 100          |
| F-2          | 2           | MC<br>0.6                | Citric acid monohydrate<br>+<br>triethylcitrate<br>0.18  | -           | to 100          |
| F-3          | 2           | NaCMC<br>0.6             | Citric acid monohydrate<br>+<br>triethylcitrate<br>0.18  | -           | to 100          |
| F-4          | 2           | HPMC<br>0.6              | Citric acid monohydrate<br>+<br>triethylcitrate<br>0.18  | 0.2         | to 100          |
| F-5          | 2           | MC<br>0.6                | Citric acid monohydrate<br>+<br>triethylcitrate<br>0.18  | 0.2         | to 100          |
| F-6          | 2           | NaCMC<br>0.6             | Citric acid monohydrate<br>+<br>triethylcitrate<br>0.18  | 0.2         | to 100          |
| F-7          | 2           | Eudragit<br>L 30 D<br>10 | PEG 6000<br>0.3  | 0.5         | to 100          |

\* Citric acid monohydrate + triethylcitrate (1:1)

carried out for each batch of product and the results averaged.

## Results and Discussion

The polymers investigated were HPMC, MC, NaCMC and Eudragit L 30 D. In preliminary experiments it was found that with the polymers HPMC and MC, coating with the spray drying technique was unsuccessful

Eudragit L 30 D as the polymer, citric acid monohydrate and triethylcitrate and PEG 6000 as the plasticizer and Aerosil 200 as the spheronizer (F-6, F-7).

For polymeric systems, it is essential that the polymer hydrates rapidly to form a gel. It is this gel formation that prevents initial dissolution of surface particles and retards the enclosed drug. An initial small burst effect

Table 2. Equations according to zero and first order kinetics for F-6 & F-7 formulations

| Formulations | Medium                          | Zero order kinetics                    | First order kinetics                                 |
|--------------|---------------------------------|--|--|
| F - 6        | pH 1.2 hydrochloric acid buffer | $y = 0.490 x - 3.861$<br>$r^2 = 0.98$  | $y = 0.012 x + 3.471$<br>$r^2 = 0.11$                |
| F - 6        | pH 7.4 phosphate buffer         | $y = 0.131 x + 23.111$<br>$r^2 = 0.35$ | $y = -9.331 \cdot 10^{-3} x + 4.877$<br>$r^2 = 0.93$ |
| F - 7        | pH 1.2 hydrochloric acid buffer | $y = 0.975 x - 0.629$<br>$r^2 = 0.98$  | $y = 0.014 x + 3.459$<br>$r^2 = 0.13$                |
| F - 7        | pH 7.4 phosphate buffer         | $y = 0.222 x + 4.778$<br>$r^2 = 0.95$  | $y = -7.156 \cdot 10^{-3} x + 4.879$<br>$r^2 = 0.85$ |

because the dried particulates were unsatisfactory by the surface and the coating properties. So the dissolution studies were done only in the formulations containing NaCMC and

is expected due to the dissolution of the crystals present on the surface of the spray dried particles (11). The water penetrates and gelling of the polymer film takes place,

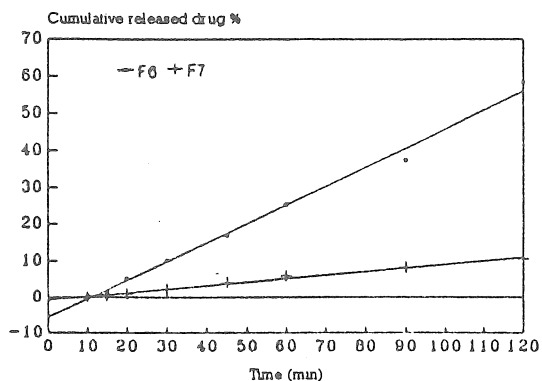


Fig.1. In pH 1.2 hydrochloric acid buffer, drug release from F-6 & F-7 formulations according to zero order kinetics

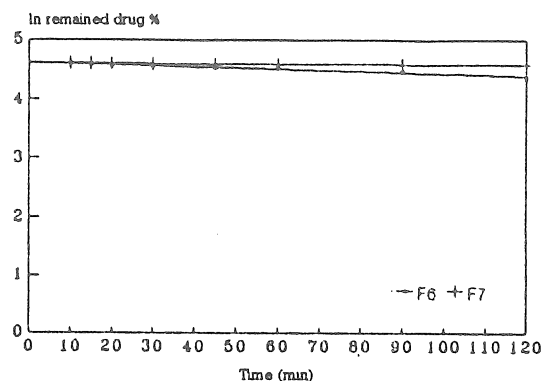


Fig.2. In pH 1.2 hydrochloric acid buffer, drug release from F-6 & F-7 formulations according to first order kinetics

increasing the thickness of the gel as the water moves inwards. Drug release would be due to the rate of drug diffusion through the gel layer. If no gelling occurs, water penetrates through the pores and drug release will then be determined by the rate of drug transfer through these pores.

The spray dried micropellets prepared in this study tended to form aggregates and on contact with water formed multi-particulate gelatinous masses. Polymer gelling, together with swelling can block up the pores and set up a diffusional barrier. The hydrophilicity of the polymer could play a major role in determining the dissolution properties of the spray dried micropellets since it controls the rate of hydration. NaCMC, which is a hydrophylic polymer, in pH 7.4 swelled and blocked up the pores and retarded the dissolution of theophylline.

Also, Eudragit L 30 D, with the addition of the plasticizer PEG 6000 retarded the drug release.

Both of the polymers gave us sustained release drug delivery profiles which are suitable results for theophylline preparations.

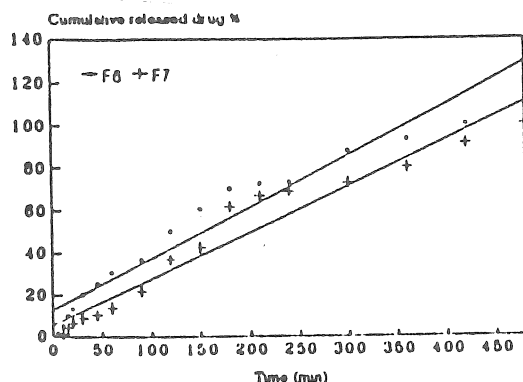


Fig.3. In pH 7.4 phosphate buffer, drug release from F-6 & F-7 formulations according to zero order kinetics

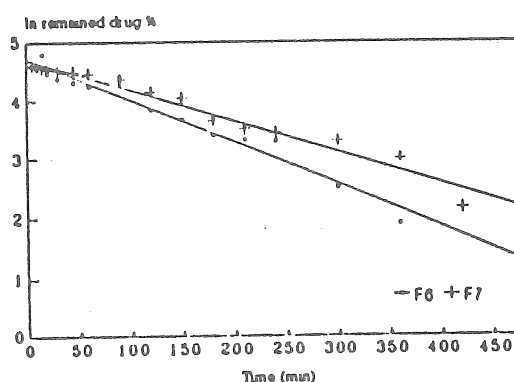


Fig.4. In pH 7.4 phosphate buffer, drug release from F-6 & F-7 formulations according to first order kinetics

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