Acta Pharmaceutica Turcica
45:23-29(2003)

Effects of Polymer Type and Granule Sizes on the Dissolutions of Naproxen Sodium Matrix Granules and Tablets

Naproksen Sodyum Matriks Granüle ve Tabletlerinin Çözünme Hızlarına Polimer Tipi ve Granüle Boyutunun Etkileri

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Abstract

The aim of this study was to investigate the effect of particle sizes of the granules prepared by various polymers on the dissolution rate of naproxen sodium matrix tablets. The tablets were prepared using matrix granules of naproxen sodium. The active substance and the polymeric materials such as hydroxypropylmethylcellulose (HPMC), carboxymethylcellulose (CMC), EUDRAGIT L 100 and EUDRAGIT RL 100 were granulated with either water or methanol to prepare the matrix dosage forms. The granules prepared with HPMC or CMC and those with Eudragit RL 100 or L 100 were analysed by sifting through sieves with 2mm to 500μm and 1mm to 125μm pores respectively. The granule fractions and the tablets prepared with these fractions were tested for dissolution rates in simulated intestinal fluid for a period of eight hours according to USP XXII rotating paddle method. In order to investigate the mechanism of the percentage release versus time profile of these tablets the results were subjected to goodness-of-fit analysis. The results showed that the tablet formulations prepared by using CMC in the particle sizes from 2mm to 710μm fitted better to the square root of time release kinetic (Higuchi equation) when compared to first-order, zero-order and cube root of time (Hixson-Crowell) release kinetics. The results of the analysis of other formulations showed a better fit to first order release kinetic.

Key words: Naproxen sodium, matrix tablet, matrix granule, HPMC, CMC, Eudragit L 100, Eudragit RS 100

Introduction

Controlled-release (CR) technology is being progressively explored in the pharmaceutical industry due to therapeutic, economic and commercial advantages. Several papers have been published on matrix-type CR dosage forms comprised of carboxymethylcellulose (CMC) (Varshosaz *et al.*,2002), hydroxypropylmethylcellulose (HPMC) (Lapidus *et al.*, 1987, Wan *et al.*, 1992, Sangalli *et al.*, 1993) or methacrylic acid co-polymers such as Eudragit L100 and Eudragit RL 100 (McGinity *et al.*, 1983, Cameron *et al*, 1987).

Naproxen sodium, (+)-6-methoxy-α-methyl-2-naphthalene acetate sodium, is a nonsteroidal anti-inflammatory drug available only as the S- enantiomer. It is effective for the relief of gout and as an anti-inflammatory/analgesic when administered two or three times a day (Dahl *et al.*, 1990). It is well absorbed orally and throughout the GI tract. The naproxen anion is bound

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intensively to plasma albumin, which results in the non-linear kinetics of naproxen sodium (or naproxen). The non-linear pharmacokinetics can be described by a two-compartment open system with first-order absorption and plasma protein binding. The non-linear pharmacokinetics result in an increased urinary excretion of naproxen and its metabolites as dose and plasma concentration increase. Due to these pharmacokinetic properties, it may be more efficient to deliver this agent at a controlled, but reduced input rate compared with an oral bolus dose occurring from an immediate-release dosage form.

The purpose of the present work was to investigate the in vitro performance of compressed matrix tablets prepared by granulating using several polymeric substances, and to determine the effect of the granule particle size on the dissolution rate. CMC, HPMC, Eudragit L 100 and Eudragit RL 100 were used as the polymeric materials to produce controlled–release dosage forms of a very highly soluble (196.7mg/mL) drug substance naproxen sodium (Chowhan, 1978).

Materials and Methods

Naproxen sodium was supplied from Kemopharm. CMC was supplied from Sigma. HPMC was obtained from Mustafa Nevzat Pharm. Co. Ltd. Eudragit L 100 and Eudragit RL 100 were supplied from Röhm Pharma (D-Darmstadt). Methanol was obtained from Sigma.

Preparation of matrix granules: Four types of granules were prepared by using, CMC, HPMC, Eudragit RL 100 and Eudragit L 100. Naproxen sodium and the polymer particles were reduced to a particle size less than 250 μm. The matrix granules containing CMC or HPMC were prepared by dissolving 2.2g naproxen sodium in 9 or 14 ml water and adding 4.4g of CMC or HPMC respectively, then mixing and granulating separately. The two kinds of the matrix granules were dried in oven (50-60°C) during 3 hours, milled and sieved through a combined sieve set (Retsch, Germany) to obtain four different particle sizes as 2-1.4 mm, 1.4-1 mm, 1mm-710 μm, 710-500 μm.

The matrix granules containing Eudragit L 100 or Eudragit RL 100 were prepared by blending 2.2g naproxen sodium and 4.4g polymer in a suitable blender and then granulating with methanol. The two kinds of the matrix granules were dried in oven (50-60°C) during 3 hours and milled and then sieved through a combined sieve set to obtain four different particle sizes as 1mm-710 μm, 710- 500 μm, 500-250 μm, 250-125 μm.

Preparation of the matrix tablets: The four different types of matrix tablets containing 412.5 mg of the matrix granules in different particle sizes as described above were prepared by compacting the granules with a hydraulic press (Perkin-Elmer) in flat-faced punches of 13 mm diameter with a compaction force of 7540 kg/cm^2 without any additives. The compaction force was applied near to 10s. Each tablet contains 137.5 mg naproxen sodium.

Dissolution studies: The in vitro dissolution was monitored according to the USP paddle method. The stirring rate was 50 rpm. Simulated intestinal fluid without enzymes (450 ml) was maintained at 37.0±0.5°C. A UV detector (Shimadzu UV 1208, Japan) was used to monitor the tablet dissolution at 263 nm (USP XXII).

Results and Discussion

The effects of the polymers and the granule particle sizes on the dissolution rate were monitored in figs 1- 4. Fig. 1 shows the dissolution results of the matrix granules and the tablets prepared by using CMC. The granule particle sizes were variable in the ranges of 2 mm to 500 μm. It was observed that the differences of the dissolution rate results between the granules and the tablets were not significant and the particle sizes of the granules were not effective on the dissolution rate of the tablets.

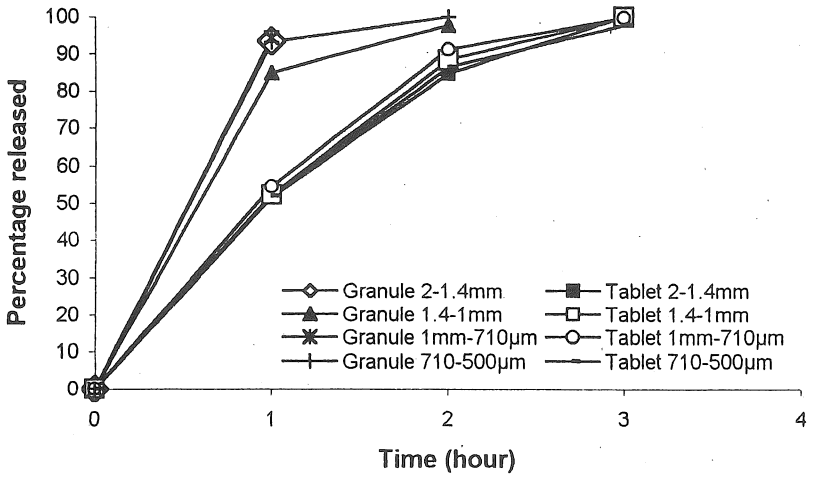

Fig. 1. Release of naproxen sodium from granules and tablets prepared with different particle sizes using CMC.

Fig. 2 demonstrates the dissolution results of the matrix granules and the tablets prepared using HPMC which indicates, the dissolution rates of the tablets were clearly less than that of the matrix granules. According to Rekkas and Papaioannou (1986), an increase in the particle size of the granules decreases the rate of dissolution. The present study showed that, an increase in particle size of naproxen sodium matrix granules from 500 µm to 2 mm resulted with an increase in % drug released.

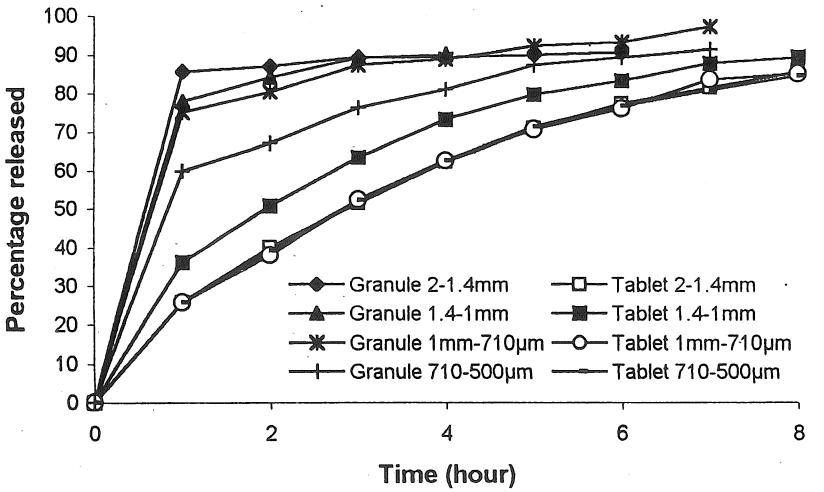

Fig. 2. Release of naproxen sodium from granules and tablets prepared with different particle sizes using HPMC.

The dissolution rates of the matrix granules and the tablets prepared with Eudragit L 100 are presented in fig.3. The particle sizes of the granules varied from 1mm to 125µm. The dissolution results of the matrix granules having four different particle size ranges were almost the same. There was an evident difference between the dissolution rates of the granules and the tablets such that the dissolution rates of the tablets were slower than that of the granules. This is

in accordance with the acceptance that the granule particle sizes of the tablets has a minor effect on the dissolution rate.

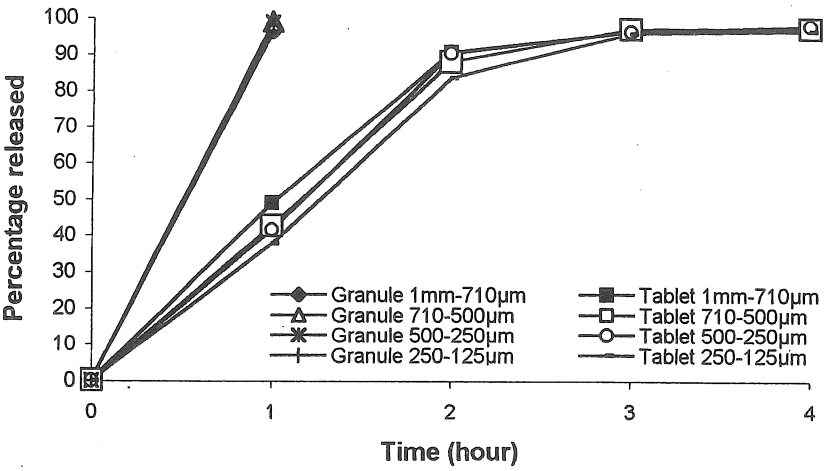

Fig. 3. Release of naproxen sodium from granules and tablets prepared with different particle sizes using Eudragit L 100.

The dissolution rates of the drug from matrix granules and the tablets prepared with Eudragit RL 100 are showed in fig. 4. The dissolution rates of the matrix granules increased with decreases in the particle sizes from 1mm to 250µm. The dissolution rates of the tablets were very low and obviously slower than that of the matrix granules. The differences between the dissolution results of the tablets prepared with various particle sizes were not observed to be very significant.

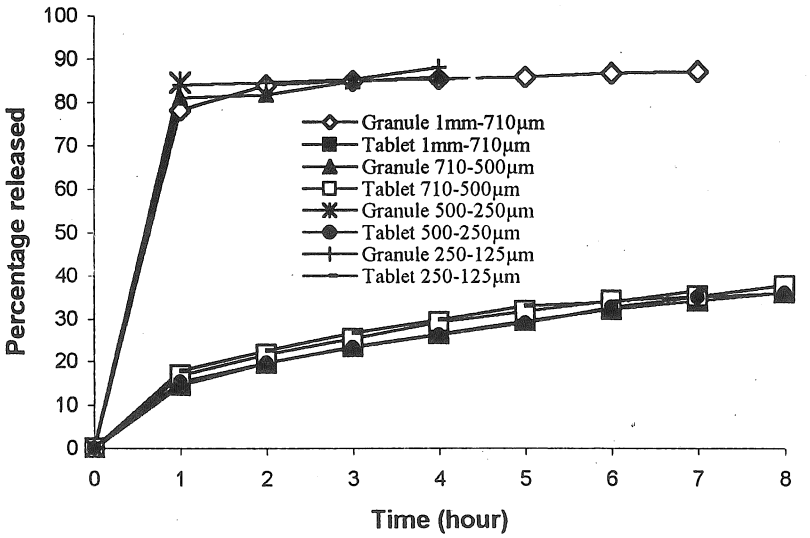

Fig. 4. Release of naproxen sodium from granules and tablets prepared with different particle sizes using Eudragit RL 100.

In order to investigate the mechanism of release of the tablets, the percent drug release versus time profile was evaluated for goodness of fit method. The details of the use of this statistical technique are given by Bamba *et al* (Bamba *et al.*, 1979a,b).

The results of the goodness of fit analysis for the tablet formulations prepared by using CMC in the particle sizes of 2mm - 710μm showed a better fit for square root of time release kinetic compared to first-order, zero-order and cube root of time release kinetics. For the all other formulations such as CMC granules with the particle sizes of 710- 500μm, HPMC, Eudragit RL 100 and Eudragit L 100 granules, the results of the analysis show a better fit for first order release kinetic compared to the other release kinetics (Table1) (Fig. 5).

Table 1.Comparison of data fits using least squares analysis of the matrix tablets.

Data fit / Formulation	First order		Zero order		Square root		Cube root	
	r^2	$\Sigma(Resd)^2/n-2$	r^2	$\Sigma(Resd)^2/n-2$	r^2	$\Sigma(Resd)^2/n-2$	r^2	$\Sigma(Resd)^2/n-2$
CMC 2-1.4mm	0.816	59711	0.955	2779	0.981	610	0.960	858
CMC 1.4-1mm	0.830	46712	0.918	3250	0.955	455	0.981	716
CMC 1mm-710μm	0.842	34840	0.889	4067	0.932	188	0.992	529
CMC 710-500μm	0.990	23	0.920	3304	0.956	317	0.997	37
HPMC 2-1.4mm	0.999	0.877	0.956	766	0.992	67	0.994	92
HPMC 1.4-1mm	0.994	1.68	0.915	1855	0.974	129	0.979	365
HPMC 1mm-710μm	0.993	2.19	0.954	733	0.990	88.2	0.991	81.9
HPMC 710-500μm	0.998	0.722	0.947	790	0.989	59	0.990	672
Eudragit L 100 1mm-710μm	0.921	115	0.713	4379	0.797	348	0.848	280
Eudragit L 100 710-500μm	0.931	95.7	0.740	3102	0.821	208	0.876	109
Eudragit L 100 500-250μm	0.968	98.2	0.718	3112	0.801	256	0.885	121.6
Eudragit L 100 250-125μm	0.945	64.3	0.775	2179	0.851	536	0.901	83
Eudragit RL 100 1mm-710μm	0.987	0.842	0.976	240	0.999	9.999	0.984	176
Eudragit RL 100 710-500μm	0.976	1.413	0.964	340	0.995	41.6	0.972	255
Eudragit RL 100 500-250μm	0.988	0.625	0.982	247	0.994	12.9	0.986	181
Eudragit RL 100 250-125μm	0.848	14.5	0.897	264	0.859	17.9	0.866	156

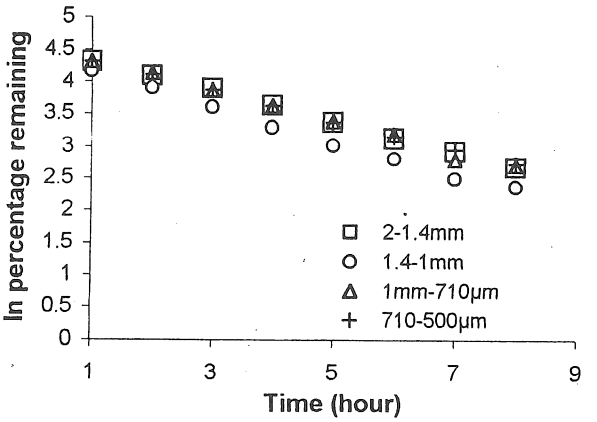

Fig. 5. First order distribution of naproxen sodium tablets prepared using HPMC with the particle sizes of 500μm-2mm.

Dissolution studies showed that the best results for sustained action were obtained from tablets prepared using HPMC. For this reason, Peppas equation (Peppas, 1985) in which the release exponent (n) characterizes diffusion mechanism was used in order to understand better the dissolution mechanism of the tablets prepared with HPMC. Except for the tablets prepared with the granule particle sizes of 1.4-1mm, the n values for all formulations were 0.59 and 0.60, which indicated that naproxen sodium release mechanism was non-Fickian (Table 2).

Table 2. Value of diffusional exponent n, based on equation $M_t/M_\infty=kt^n$.

Formulation	n	r^2
HPMC (2-1.4mm)	0.59	0.992
HPMC (1.4-1mm)	0.445	0.986
HPMC (1mm-710μm)	0.60	0.992
HPMC (710-500μm)	0.59	0.90

Özet

Bu çalışmanın amacı, naproksen sodyum matrix tabletlerinin çözünme hızı üzerine, değişik polimerlerle hazırlanmış granülelerin partikül büyüklüklerinin etkisini araştırmaktır. Tabletler naproksen sodyum matriks granüleleri kullanılarak hazırlanmıştır. Etken madde ve hidroksipropilmetilselüloz (HPMC), karboksimetilselüloz (CMC), EUDRAGIT L 100, EUDRAGIT RL 100 gibi polimerik materyallerin su ya da metanol ile granüle haline getirilerek matriks dozaj formları elde edilmiştir. HPMC veya CMC içeren granüleler 500μm ile 2mm arasında delik çapına sahip eleklerle, EUDRAGIT L 100 veya EUDRAGIT RL 100 içeren granüleler ise 125μm ile 1mm arasında delik çapına sahip eleklerle analiz edilmiştir. Granüleler ve bunlardan hazırlanan tabletlerin çözünme hızları 8 saat boyunca USP XXII döner palet metoduyla suni barsak vasatında test edilmiştir. Bu tabletlerin, zamana karşı yüzde salım mekanizmaları uyum iyiliği analizlerine göre değerlendirilmiştir. CMC kullanılarak 710μm ile 2mm arasında partikül büyüklüklerinde hazırlanan tablet formülasyonları için birinci derece, sıfırıncı derece ve Hixson-Crowell kinetikleriyle karşılaştırıldığında Higuchi eşitliği daha iyi uyum göstermiştir. Diğer tüm formülasyonlar için ise analiz sonuçları birinci derece salım kinetiğine daha iyi uyum göstermiştir.

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Accepted: 22.04.2002