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Effect of Formulation and Process Variables on the Dissolution Profile of Naproxen Sodium from Tablets

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ABSTRACT

Results of this investigation revealed some important formulation characteristics of naproxen sodium. Tablets made from the granules, prepared by wet granulation method using water, showed a significant decrease in solution as compared to those made by dry blending method. During wet granulation, heat was evolved due to the hydration of naproxen sodium resulting in the retardation of dissolution. The pseudo-polymorphism and hydration is being investigated by Bansal et. al. (1). In addition, when polyvinyl pyrolidone (PVP K-90) was used instead of PVP K-30, the dissolution was further retarted. Addition of cross carmellose sodium (Ac-Di-Sol) did not change the dissolution behavior of these tablets. When naproxen sodium was granulated with water, a decrease in dissolution rate was observed as mixing time was increased from 5 minutes to 15 minutes. The increase in hardness of the tablet from 10 Kp to 18Kp did not alter the dissolution profile of naproxen sodium. When granulation was prepared using a low shear mixer (Planetary mixer) versus a high shear mixer (T.K. Fielder), the resultant tablets exhibited similar dissolution and physical chemical properties.

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INTRODUCTION

Naproxen sodium, an anti-inflammatory agent, is known for the last few decades and is an active ingredient of NAPROXEN SODIUM^{R} tablets (1). The effect of formulation and process variables in the optimization of granulation and compression processes has been recognized (2-4). Effect of excipients and granulating fluids on the release properties of medicinal agents has also been studied in the past (2-7), however, the effect of formulation and process variables in the manufacturing of naproxen sodium tablets has not been documented. The purpose of this investigation was to study the effect of water granulation versus dry mixing, binder, and disintegrant (Ac-Di-Sol) on the dissolution and physical chemical properties of the tablets.

MATERIALS AND METHODS

Tablet formulations were prepared according to the compositions described in Table 1. Dry blends (Formulation #1) and wet granules were prepared by mixing naproxen sodium and Avicel pH 101 for 15 minutes in a planetary mixer.

The granules were dried at 50°C and were milled, using fitzpatric mill fitted with screen #2, at a medium speed. Sieve analysis showed that in all cases 50 ± 5% of the powder was retained on a 100 mesh sieve and 50 ± 5% was under 100 mesh. The milled granules were mixed with the talc and magnesium stearate for three minutes. The tablets were compressed on a 16-station rotary machine (Manesty Beta-Press) at an average weight of 750 mg using capsule shaped concave punch and die sets.

Dissolution studies were carried out using the USP Dissolution Apparatus equipped with paddles at 50 rpm employing 0.1M phosphate buffer (pH 7.4) as dissolution medium. Samples were withdrawn at 10, 20, 30, 45, 60 and 75 minute intervals and were analyzed spectrophotometrically at a wave length of 332 nm against the standard solution.

TABLE 1. COMPOSITIONS OF SEVERAL DIFFERENT FORMULATIONS OF NAPROXEN SODIUM USED IN THIS STUDY.

	Composition, mg/Tablet							
Ingredient	1	2	3	4	5	6	7	8
Naproxen Sodium	550	550	550	550	550	550	550	550
Avicel pH 101	164	164	164	126	126	164	164	164
PVP K-30, USP	-	20	-	20	-	20	20	20
PVP K-90, USP	-	-	20	-	20	-	-	-
Purified Water*, USP	-	110	110	110	110	125	150	175
Ac-Di-Sol	-	-	-	38	38	-	-	-
Talc, USP	8	8	8	8	8	8	8	8
Magnesium Stearate	8	8	8	8	8	8	8	8
Total Weight	730	750	750	750	750	750	750	750

RESULTS AND DISCUSSION

As described in Table I, several different formulations of naproxen sodium were prepared to investigate the effect of water as granulating fluid, cross carmellose sodium (Ac-Di-Sol) as disintegrant and polyvinyl pyrolidone (PVP K-30 and PVP K-90) as binder. The use of water as granulating fluid revealed some interesting phenomenon. During granulation with water an exothermic reaction occurred and the resultant tablets exhibited a slower dissolution as compared to those made without using any water (Figure 1). When the granulations were made with increasing amounts of water, the corresponding tablets showed a decrease in dissolution respectively. This phenomenon indicated a possibility of hydration of naproxen sodium in the granulation which resulted in the observed retardation of dissolution. The hydrates, solvates or pseudopolymorphs of naproxen sodium are not reported in the literature. A monohydrate of naproxen sodium has been isolated and pseudo-polymorphism is under investigation. (Results of this study are the subject of a separate publication). Based on these results, it is apparent that the use of higher quantities of water converted more and more naproxen sodium into a hydrated form which had less affinity for water than anhydrous form and, therefore, a retardation in dissolution was observed.

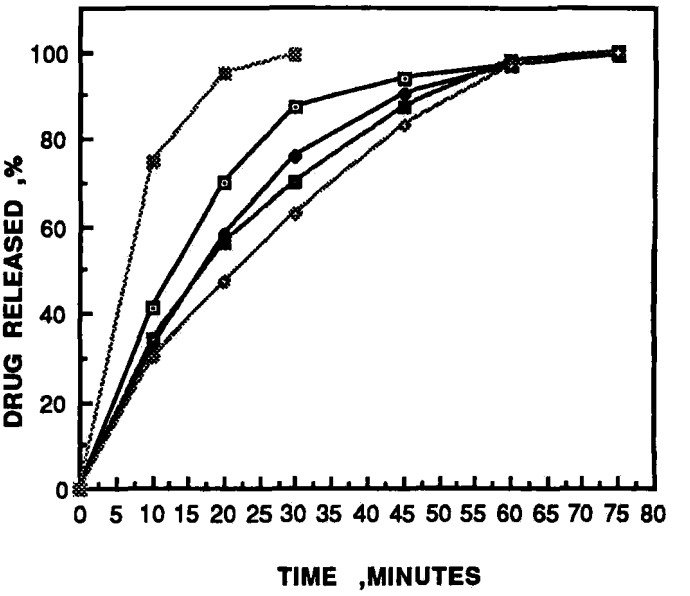

FIGURE 1

Dissolution Profile of Naproxen Sodium Tablets. Prepared Using Different Amount of Water, Dry Blending, 110g Water, 125g Water, 150g Water, 175g Water.

Furthermore, the tablets made from the granulation using PVP K-90 exhibited a slower dissolution as compare to those made using PVP K-30 as binder (Figure 2). This is probably due to the higher molecular weight and viscosity of PVP which produced harder granules and greater particle to particle binding. The use of a disintegrant Ac-Di-Sol^{R} did not change the dissolution profile of these tablets made from either of the two binders (Figure 2). These results indicate that the dissolution was controlled by the crystal form of naproxen sodium (anhydrous or hydrate) and not by the disintegration properties.

Studies were carried out to evaluate the effect of mixing time, during granulation, on the release of naproxen sodium from tablets. Results (Figure 3) show that an increase in mixing time

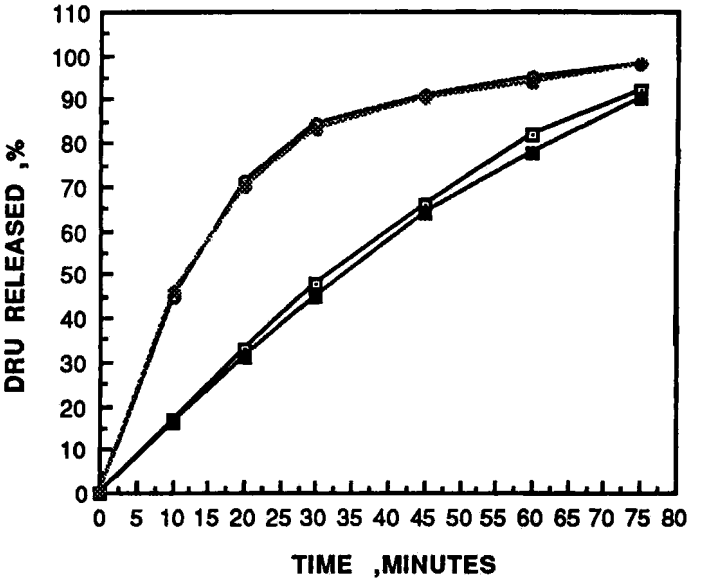

FIGURE 2

Dissolution Profile of Naproxen Sodium Tablets prepared Using Different Binders, —o— PVP K-30, —⊗— PVP K-30/Ac-Di-Sol, —▫— PVP K-90, —■— PVP K-90/Ac-Di-Sol.

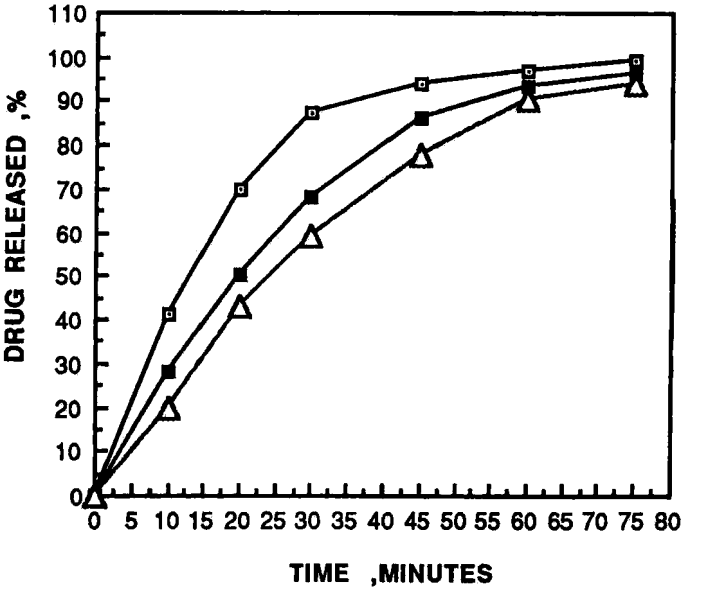

FIGURE 3

Dissolution Profile of Naproxen Sodium Tablets Prepared From Granules Mixed For 5, 10 and 15 Minutes, —▫— Mixing Time 5 Minutes, —■— Mixing Time 10 Minutes, —△— Mixing Time 15 Minutes.

from 5 minutes to 15 minutes during granulation resulted a corresponding decrease in the release rate of naproxen sodium from tablets. This observed behavior may be explained based on the hydration of naproxen sodium. As the mixing time was increased, the moisture came in contact of naproxen sodium to form more and more of the hydrate resulting in a decrease in it's release from tablets. Furthermore, when tablets were compressed between the hardness of 10-18 Kp, they showed no detectable differences in their release profiles.

In conclusion, the importance of pseudopolymorphism on the granulation process of anhydrous naproxen sodium and its impact on the release from tablets has been demonstrated. Thus, in order to develop a reproducible process, the amount of granulation fluid and mixing time must be optimized.

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