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Enteric Coated Film Tablets of Naproxen Sodium

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Summary : *Naproxen sodium (NS) has analgesic, antipyretic and anti-inflammatory activity. It is rapidly absorbed after oral and rectal administration. It is a nonsteroidal anti-inflammatory (NSAI) drug and it is a derivative of phenyl propionic acid. The aim of this study is to prepare film coated tablets of NS to decrease its adverse effects in the gastrointestinal system. Core tablets (CoT) were prepared by direct compression technique. Hardness, disintegration control, weight deviation, friability, in-vitro dissolution test and content uniformity of the active substance were performed in core tablets. Apparatus II (USP 24) in dissolution test and UV spectrophotometric method for the assay of the active substance were used. Spray technique was used to prepare enteric coated film tablets of NS. Eudragit L 100-55, S100, L100 were used in different concentrations as coating materials. PEG 4000 was chosen as plastifier. Assay method was validated. Film coated tablets did not disintegrate in simulated gastric medium (SGM) (pH 1.2) for about 2 hours, but they disintegrated in simulated intestinal medium (SIM) in 20-30 minutes. Approximately 50-97 % NS was dissolved in SIM (pH 7.4) in 55 minutes.*

Key Words: *Naproxen sodium, Enteric coated film tablets, Eudragit L 100-55, S 100, L 100*

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Naproksen Sodyumun Enterik Kaplı Film Tabletleri

Özet : *Naproksen sodyum (NS); analjezik, antipiretik ve antienflamatuar etkiye sahiptir. Oral ve rektal olarak alındıktan sonra hızlı absorbsiyona uğrar. Nonsteroidal yapıda bir maddedir ve fenil propionik asit türevidir. Çalışmanın amacı NS'nın midedeki yan etkilerini azaltmak için enterik kaplı film tablet hazırlamaktır. Direkt basım tekniği ile çekirdek tabletler hazırlanmıştır. Çekirdek tabletlerde sertlik, dağılma kontrolü, ağırlık sapması, ufalanma-aşınma, in vitro çözünme hızı tayini ve etkin madde miktar tayini yapılmıştır. In vitro çözünme hızı testlerinde Apparatus II (palet) yöntemi (USP 24) ve etkin madde miktar tayininde ise UV spektrofotometrik yöntem uygulanmıştır. Püskürtme tekniği kullanılarak NS'nin enterik kaplı film tabletleri hazırlanmıştır. Kaplama materyali olarak Eudragit L100-55, Eudragit S 100 ve Eudragit L 100, değişik oranlarda kullanılmıştır. Polietilen glikol (PEG) 4000 de plastifiyan olarak seçilmiştir. Miktar tayini yöntemi valide edilmiştir. Film kaplı enterik tabletler yapay mide ortamında dağılmamıştır (yaklaşık 2 saat), ancak barsak ortamında 20-30 dakikada dağılmıştır. Yaklaşık %50-97 oranında NS 55 dakikada barsak ortamında çözünmüştür.*

Anahtar kelimeler : *Naproksen sodyum, Enterik kaplı film tablet, Eudragit L 100-55, S 100, L 100*

INTRODUCTION

Coating may be applied to tablets to protect the active ingredients from light and the atmosphere; coatings may also mask unpleasant tastes and odours or prevent contact with a substance of an irritant or potentially sensitising nature. The purpose of enteric coating is to control the location of drug release in the body whereas in sustained-release tablets the aim is to control the rate of release by suitable coatings on either the granules or the tablet cores[1-3].

The acrylic polymers Eudragit L and S are capable of forming salts in neutral to weakly alkaline environments and dissolve in the intestines. In the acid pH range they are impermeable to water. They consequently provide full protection against gastric acid and ensure drug release in the small intestine[4]. Jac-

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queline et al[5] investigated the enteric coating properties of Eudragit®, Aquateric® and Cellulose Acetate Trimellitate (CAT) applied to capsules. CAT coatings were not very resistant at low pH values. Liquid water permeation into the capsule was low with Eudragit® L 100-55 coatings, intermediate with Aquateric® and high with CAT. Nykänen et al[6] investigated whether enteric-coated tablets could be made from enteric coated matrix granules and drug release targeted to the colon. Eudragit S and hydroxypropyl methylcellulose acetate succinate (HPMCAS) Aquat AS-HF were used as enteric polymers. Drug release rates were studied at different pH levels and drug absorption was studied in bioavailability tests. Pulsatile release tablets with ethylcellulose and Eudragit L as film coating materials and cross-linked polyvinylpyrrolidone in the core tablets was studied by Fan et al[7]. Pancreatin pellets, placebo pellets and tablets containing vitamin B_2 were coated with various aqueous and organic enteric polymers, HPMCAS, hydroxypropyl methylcellulose phthalate (HPMCP), Eudragit® L 100-55, L 30 D-55, Cellulose Acetate Phthalate (CAP), CAT, carboxymethyl ethylcellulose (CMEC) and polyvinyl acetate phtlate (PVAP) were comparatively investigated and tested for storage stability by Karl and Karoline[8]. When applied to vitamin B_2 tablets, Eudragit® L 100-55, PVAP and HPMCAS proved to be quite stable aqueous enteric coatings, whereas CAP and CAT were unstable. Theophylline pellets were coated with Eudragit® RL 30D and NE 30D, using an Uni-Glatt fluidized-bed apparatus by Rasmane et al[9]. The anatomical location and disintegration behaviour of a naproxen enteric-coated tablet formulation was evaluated in 12 healthy cases by Ian et al[10]. Disintegration of the tablet did not commence until the tablet had passed from the stomach into the small intestine. Enteric coated naproxen tablets were prepared and investigated by different research groups[11-13]. The extent of absorption is the same for enteric coated and plain tablets. The onset of absorption is delayed as a result of retention of larger particles in the stomach and more so when taken along with food.

Naproxen has analgesic, anti-inflammatory and antipyretic properties; it is an inhibitor of cyclooxygenase. Both naproxen and NS are used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis, in mild to moderate pain such as dysmenorrhoea, migraine and some musculoskeletal disorders and in acute gout. In the treatment of rheumatic disorders, the usual dose of naproxen and NS is the equivalent of 500 mg to 1g of naproxen daily either as a single dose or in divided doses. Naproxen and NS are rapidly absorbed from the gastro-intestinal tract. Peak plasma concentrations are attained about 1 to 2 hours after ingestion of NS. Food reduces the rate but not the extent of absorption[14-15]. Piera et al[16] studied physical characterization of NS hydrate and anhydrate forms. When stored in up to 43% relative humidity, NS anhydrate shows good stability, whereas with an increase in relative humidity it is hydrated. Novel polyoxyethylene esters of ketoprofen, naproxen and diclofenac were synthesized and evaluated as potential dermal prodrugs by Francesco et al[17]. Marc et al[18] investigated the *in vitro* and *in vivo* evaluation of four different aqueous polymeric dispersions for producing an enteric coated tablet. NS was used as the model drug. Eudragit L, CAP and CAT were selected for enteric coating. It was found that all of the enteric coat formulations performed satisfactorily during initial *in vitro* disintegration and dissolution testing.

In this study, NS enteric coated film tablets were prepared to decrease the local gastric irritation by the spray technique. Core tablets were prepared by direct compression technique. Hardness, disintegration control, weight deviation, friability, *in-vitro* dissolution test and content uniformity of the active substance were performed in core tablets. Apparatus II (USP 24)[19] in the dissolution test and UV spectrophotometric method for the assay of the active substance were used. Spray technique was used to prepare enteric coated film tablets of NS. Eudragit L 100-55, S100, L100 were used in different concentrations as coating material. PEG 4000 was used as a plastifying agent. Assay method was validated. Film tablet specifications were determined and evaluated statistically.

EXPERIMENTAL

1. Chemicals

NS (Bilim, Turkey), Eudragit L 100-55 (RöhmPharma, Germany), Eudragit L 100 (RöhmPharma, Germany), Eudragit S 100 (RöhmPharma, Germany), PEG 4000 (Merck, Germany), Sodium Dihydrogen Phosphate (Carlo Erba, Italy), Pepsin (Riedel-de Haën, Germany), Microcrystalline Cellulose pH 101 (FMC Corporation, U.S.A.). All chemicals were of analytical grade.

2. Apparatus

UV Spectrophotometer (UV-Visible Recording Spectrophotometer, UV 160 A, Shimadzu, Japan), tablet machine (Korsch AR 400, Erweka, Germany), pH meter (Orion, Shimadzu, Japan), dissolution and disintegration test apparatus (Aymes, Turkey), friabilator (Roche, Switzerland), hardness apparatus (Monsanto), pulverizer (Ildam, Turkey), cubic mixer (Erweka, Germany).

3. Preparation of core tablets

Content of core tablet was NS 550.0 mg, Microcrystalline Cellulose 155.0 mg, PVP (K30) 55.0 mg and Magnesium stearate 15.0 mg. All ingredients were mixed in a cubic mixer and core tablets with a weight of 775.0 mg were prepared on an instrumented single-punch tablet machine by direct compression technique. The following tests were applied to the tablets; Amount of NS, crushing strength, diameter-height ratio, weight deviation and friability. Tablet weight uniformity was calculated according to USP 24 and tablet thickness was determined using a micrometer. Tablet hardness tests were carried out using a Monsanto hardness tester. For friability tests, twenty tablets were weighed (W_1) and rotated at one hundred revolutions for 4 min in a Roche friabilator. The tablets were then reweighed (W_2) and the percentage friability (%F) was calculated. Results are given in Table 1.

4. Film coating

Four film coating solution were prepared.

I.	Eudragit L 100-55	5.00%	II.	Eudragit S 100	5.00%
	Ethanol (96%)	86.25%		Ethanol (96%)	86.25%
	PEG 4000	1.25%		PEG 4000	1.25%
	Distilled Water	7.50%		Distilled Water	7.50%
III.	Eudragit L 100	5.00%	IV.	Eudragit L 100	2.50%
	Ethanol (96%)	86.25%		Eudragit S 100	2.50%
	PEG 4000	1.25%		Ethanol (96%)	86.25%
	Distilled Water	7.50%		PEG 4000	1.25%
				Distilled Water	7.50%

Core tablets were separately coated with these solutions by the spray technique. Spray rate was 0.5mL/min at room temperature. After coating, film coated tablets specifications as average weight, amount of NS, crushing strength, disintegration time and coating thickness were investigated. Results are shown in Table 2. Coating thickness was calculated using equation 1 and 2[3].

$$S = \pi [d\,h + (d^2/2)] \qquad \text{Equation 1.}$$

S= Tablet (oblongs) surface area, h= tablet height, d= tablet diameter

l = Polymer weight(g) xTablet weight(g) x 100000 / batch size(g) x tablet surface (mm^2)

$$l = \text{Polymer weight per } cm^2 (mg/cm^2) \qquad \text{Equation 2}$$

5. Determination of NS amount in tablets

A spectrophotometric method was used for the NS assay. 500 mg NS was accurately weighed and dissolved in phosphate buffer pH 7.4 and the volume was adjusted to 100 mL. Six samples of 0.2-1.2 mL were taken from this stock solution and diluted to 100 mL with the phosphate buffer pH 7.4. Absorbance of these solutions were measured at 230.0 nm. Regression equation and regression coefficients were calculated to be y=3.1101x-0.0060 (y = Concentration ((g/mL), x = Absorbance) and r = 0.9994, respectively. Ten tablets were finely powdered and 879 mg (corresponding to average one tablet weight) was dissolved in the phosphate buffer pH 7.4 and the

volume was adjusted to 100 mL and filtered. 0.05 mL sample was taken from this solution and diluted to 100 mL with the phosphate buffer pH 7.4. Absorbance of these samples was measured at 230 nm and amount of NS was calculated by using the regression equation.

6. Validation of UV spectrophotometric method

Validation of an analytical method is the process by which it is established, by laboratory studies, that the performance characteristics of the method meet the requirements for the intended analytical applications. The validation of the types of methods are Accuracy, Precision, Specificity, Detection limit, Quantitation limit, Linearity and Range[19-21].

Precision: The precision of an analytical method is the degree of agreement among individual test results when the method is applied repeatedly to multiple sampling of a homogenous sample. 0.50, 1.50 and 3.00 µg/mL solutions were prepared using stock solution of NS. The peak responses of these samples were measured. The standard deviation or relative standard deviation (coefficient of variation) of a series of measurements was calculated. The same procedure was carried out on different days (Table 3).

Accuracy: The accuracy of an analytical method is the closeness of the test results obtained by that method to the true value. 0.50-3.00 µg/mL solutions were prepared using stock solution of NS. The peak responses of these samples were measured. Regression equation and regression coefficients were then calculated. Accuracy was calculated as the percentage of recovery by the assay of the known added amount of analyte (three concentrations: 0.5, 1.5, 3.0 µg/mL) in the sample using the regression equation (n=6) (Table 4).

7. *In vitro* dissolution studies

Dissolution tests were performed according to the paddle method described in USP 24, Apparatus II. 900 mL SGM without enzymes and SIM were used as the dissolution media (USP 24). SGM was the dissolution medium for the initial 2 hr period and then SIM for the following 4 hr at 37±0.5°C and 50 rpm. The amount of NS was determined according to the spectrophotometric method mentioned above. Dissolution profiles of film tablets are shown in Fig.1.

RESULTS AND DISCUSSION

The physical characteristics of NS uncoated tablets are given in Table 1. These tablets provided good weight uniformity and friability (F< 1.0%). These results were in accordance with the pharmacopoeia limits (USP 24).

Table 1. Uncoated tablet specification (± SD)(n=6)

Amount of NS(mg)	526.5728±5.7000
Average tablet weight(mg)	806.00±2.17
Hardness (kg)	2.400±0.875
Friability (%)	0.2074
Disintegration time	10.0 min(in SGM)

After coating, coated tablet specifications were also determined and the results are given in Table 2. Uncoated tablets disintegrated in SGM in 10 min. Coated tablets of F I-F IV did not disintegrate in SGM within 2 hr. Dissolution studies were carried out on coated and uncoated tablets and dissolution profiles are given in Figures 1 and 2. According to dissolution re-

Table 2. Coated tablets specifications (± SD)(n=6)

Specifications	F I	F II	F III	F IV	CT
Amount of NS(mg)	496.66±2.35	493.11±6.75	504.68±10.27	499.22±13.44	250.00±0.80
Average tab. weight(mg)	895.44±2.50	882.76±2.60	899.08±2.30	881.41±2.10	299.00±1.01
Hardness (kg)	2.50±1.12	2.40±0.97	2.60±0.51	2.50±0.25	3.60±1.20
Disintegration time in SGM (min)	none	none	none	none	none
Disintegration time in SIM (min)	26.00±3.56	30.00±5.11	29.00±2.82	27.00±1.63	15.00±4.76
Coating thickness (mg/cm^2)	90.12±5.86	90.07±4.89	90.38±3.88	89.71±6.65	-

sults, NS in uncoated tablets totally dissolved in SGM, whereas no amount of NS in coated tablets dissolved in SGM. A great amount of NS (in F I 96.63±3.60%, F II 96.31±0.89%, F III 93.49±2.75%, F IV 97.24±1.75% and commercial tablet (CT) 98.85±1.76%) dissolved in SIM in 60 min.

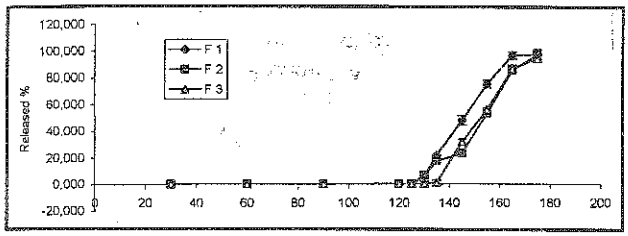

Figure 1. Dissolution profiles of F I, F II and F III.

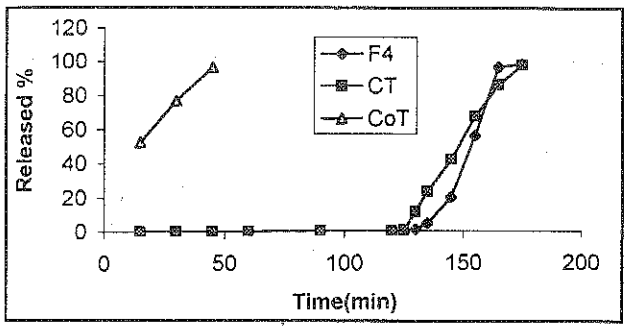

Figure 2. Dissolution profiles of F IV, CT and CoT.

Table 3. Repeatability and precision of UV-Spectrophotometric assay (RSD %)

Concentration (µg/mL)	Medium: phosphate buffer pH 7.4
Repeatability (day = 3, n=6)	
0.50	0.0183
1.50	0.0263
3.00	0.0092
Precision (day = 3, n=6)	
0.50	0.0183
1.50	0.0261
3.00	0.0048

Table 4. Accuracy results (n=6)

Regression equation	Regression coefficient	Recovery values
y = 3.2250 x + 0.0001 (1.day)	0.9994	100.30 ±0.15% (for 0.5 µg/mL)
y = 3.1101x - 0.0060 (2.day)	0.9963	99.85±0.11 % (for 1.5 µg/mL)
y = 3.2732 x - 0.0149 (3.day)	0.9994	100.15±0.09 % (for 3.0 µg/mL)

y = Concentration (µg/mL), x = Absorbance

In the validation parameters, the RSD for the sample preparation step might be approximately 1% [20,21]. As shown in Table 3, these results are suitable for method validation. Reproducibility refers to the use of the assay method for NS in different laboratories, as in a collaborative study. An important step in the validation of any analytical method is the establishment of the relationship between released % (y) and the concentration of the analyte (x) and the method may be calibrated. When the correlation coefficient was above 0.9990, the assay method was acceptable. The satisfying recoveries confirmed the suitability of the proposed method for the routine analysis of NS in pharmaceuticals (Table 4)[20,21].

Our results demonstrated that disintegration of the film tablets and dissolution of NS did not occur until the tablet had passed out of the SGM into the SIM. Therefore, these formulations will provide protection of the gastric mucosal lining from direct exposure to NS[10-12]. Thus, Gastro-intestinal adverse effects of NS are decreased. Dissolution studies carried out on Eudragit L-100, L-100/55, S-100 and their mixture coated tablets indicated that the release profiles depend not only on the physicochemical properties of the drug, particularly solubility, but also on the additive eudragit resin in dry film. Moreover, the integrity of coating material and hence the release rates, were found to be independent of the pH of the dissolution medium. According to our results, these film tablets were found to be suitable.

The increasing application of film coating to solid dosage forms and insufficient knowledge of their intrinsic characteristics have highlighted the need to adopt a fundamental approach in finding solutions to the problems encountered in film-coating practice. Considerable improvements in the properties of existing film-coating systems would be more readily achieved if adequate information on interaction phenomena is available. This approach may be less time consuming and more cost-effective than synthesizing entirely new polymers.

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