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INVESTIGATIONS ON ENTERIC COATED TENOXICAM TABLETS

ENTERİK KAPLI TENOKSİKAM TABLETLERİ ÜZERİNDE İNCELEMELER

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Tenoxicam, a tienotiazine derivative nonsteroid anti-inflammatory agent of oxicam class, is used in articular and extra-articular disturbances. One of the most important side effects of tenoxicam is its irritative effect on stomach mucosa like all other anti-inflammatory drugs. In order to overcome such problems, tenoxicam containing tablets were enteric coated with variours enteric film coating agents such as CAP, CAT, Aquateric, and Eudragit L-100 in this study. The release profiles of enteric-coated tenoxicam tablets were investigated in a buffered medium at different pH values. It was observed from the release profiles that pH affects the solubility of the drug substance and disitegration of the coating materials. The highest dissolution rate was obtained for the tablets coated with Aquateric.

Oksikam sınıfından bir tiyenotiyazin türevi non-steroid anti-enflamatuvar ajan olan tenoksikam, artikular ve extraartikular rahatsızlıkların tedavisinde kullanılır. Tenoksikamın en önemli yan etkilerinden biri, tıpkı diğer anti-enflamatuvar ilaçlarında olduğu gibi mide mukozası üzerinde irritan etkidir. Bu çalışmada, çeşitli enterik film kaplama materyalleri (CAP, Aquateric, Eudragit L-100) ile kaplandı. Kaplı tabletlerden etken maddenin serbestleşme profilleri tamponlu ortalama farklı pH'larda incelendi. Etken madde salınım profilleri, pH'nın ilacın çözünürlüğü ve kaplama materyalinin dağılımı üzerinde etkili olduğunu göstermiştir. En yüksek çözünürlük hızı, Aquateric ile kaplı tabletlerde elde edilmiştir.

Keywords: Enteric coating: Tenoxicam; Film coating; Aquateric; Eudragit L-100; CAP; CAT

Anahtar sözcükler: Enterik kaplama; Tenoksikam; Film kaplama; CAP; CAT; Eudragit L-100; Aquaterik

Introduction

Gastric irritation is one of the most important side effects of oral dosage forms (1-4). This problem can be overcome by introducing enteric coating to this route (5-7). It is well-known that enteric coated oral dosage forms dissolve in intestinal fluid rather than gastric fluid, consequently, avoiding gastric irritation (5-7). Enteric-coated dosage forms may be prepared by means of enteric coating tablets, pellets, or microspheres (4-7). Such tablets have better advantages than conventional ones as they dissolve in intestinal media rather than gastric and hence, improve patient compliance (4).

In recent years, studies on formulating oral solid dosage forms to provide enteric release of active ingredients have shown great progress. Various polymers have been used in preparation of enteric coated dosage forms (4,5). Generally, these polymers are pH sensitive in terms of dissolution rate and are insoluble in strong acidic media. Optimum pH for their solubility ranges between 4.5-7.0. Presence of carboxyl groups which are nonionized at acid pH may be the cause of such phenomenon. These characteristics of polymers provide rapid dissolution in small intestine with mild acidic-to-neutral environment, thus preventing their release in gastric fluids (4, 5).

The most widely used enteric-coating polymers are acrylic and cellulosic derivatives (1-5, 8-13). Since acrylic polymers (Eudragit L, S, LS) have limitations due to their reactive acidic groups and interaction with basic drugs (14), some enteric cellulosic derivatives have also been selected to prepare enteric-coated tablets in this study for comparison. Cellulose acetate phthalate (CAP) is the most widely used enteric coating polymer in preparation of enteric-tablets (15) because and exhibits stability for at least 6 months when used for tablet coating. Another polymer used in this study, Aquateric, is a product of CAP which forms upon hydrolysis and has been used for tablet coating. Considering cellulose acetate trimellitate (CAT), which is soluble at a low pH (pH 5.0).there is quite limited evidence in the literature on the use of this polmer in the field of enteric-dosage forms (4, 16-20).

Tenoxicam, (4-hydroxy 2-methyl N-(2-pyridyl)-2H-thieno [1, 2] thiazine-3-carboxamide 5, 1-dioxide) (TNX), has been used as an analgesic and anti-inflammatory drug perorally for the treatment of rheumatic disorders (20-28).

However, TNX exhibits side effects that cause irritation on stomach mucosa upon p.o. administration in the form of a tablet or a hard gelatin capsule (29-32). In this study TNX was selected as an active ingredient and efforts have been directed to the development of enteric-coated tablets containing this compound. Desing of such a dosage form can reduce gastric side effects by providing release in the intestinal fluids.

The main objective of this study has been to desing enteric-coated tablets containing TNX, to evaluate their dissolution profiles, and to compare all these data with those of commercialy available conventional tablets.

Materials and Methods

TNX was obtained from Roche R, Istanbul, Turkey. CAT was bought from Eastman Kodak, USA and CAP was provided from Takeda, USA. Eudragit L-100 was bought from Röhm Pharma GmbH, Germany. Aquateric was from Seletchemie, Germany. Triacetin, ethyl acetate, dibuthyl phthalate, diethyl phthalate, Tween 80, magnesium stearate, potassium & dihydrogen & phosphate, acetone, sodium hydroxide, alcohol, and n-hexane were of analytical grade and used as received.

Assay of TNX In Core Tablets

TNX contents of core tablets obtained from a pharmaceutical company to coat with an enteric-polymer were determined spectrophometrically. The stock solution of TNX was prepared at 100 mcg ml^{-1} concentration in alcohol-phosphate buffer (1:24). 0.2-20 ml aliquots were taken from this solution and their volumes were diluted upto 10 ml with the same solvent in volumetric flasks. The absorbances of the yellow-colored solutions were measured spectrophotometrically at 366 nm.

Preparation of enteric-coated TNX tablets

Core tablets containing TNX were provided from Roche R and were coated with various polymers (Aquateric, CAP, CAT, Eudragit L-100) using a Wurster apparatus.

CAP and CAT solutions for coating

CAP (CAT)	8 g
Diethyl phthalate	2 g
Ethyl acetate	45 g
Isopropyl alcohol	45 g

Ethyl acetate and isopropyl alcohol were mixed in a beaker using a mechanical mixed. CAP (CAT) was added to this mixture and the stirring procedure was continued. Following the formation of a homogenous coating solution (CAP or CAT), diethyl phthalate was added. The so obtained coating solution was kept at room temperature prior to the coating process. The weight of the core tablets increased 8% upon coating with CAP or CAT.

Aquateric solution for coating

Aquateric	12 g
Triacetin	4 g
Tween 80	0.1 g
Distilled water	83.9 g

Triacetin was dispersed in distilled water in a beaker. Tween 80 was added to this dispersion while stirring, followed by the addition of Aquateric in small potions. Core tablets were coating with CAP (1%) prior to the were coated with Aquateric since it was not desired to coat tablets with a water-based coating agent. The weight increase of the core tablets following the coating process was 6-8%.

Eudragit L-100 solution for coating

Eudragit L-100	7.3 g
Dibuthylphthalate (DBF)	1.5 g
Talc	1.8 g
Isopropyl alcohol	89.4 g

Eudragit L-100 was dissolved in isopropyl alcohol by the aid of a mechanical mixer at 300rpm. DBF and talc were added and mixed throughly and stirring was continued throughout the coating process. 6-9% of weight increase was obtained upon coating of core tablets.

Coating of core TNX tablets

The air inlet was kept at 50°C throughout the process.

Quality Control Test (QCTs) performed on enteric coated TNX-tablets

i. *Visual:* Color, shape, and the logo of the manufacturing company on the tablets were visually inspected prior to and following the coating process.

ii. *Odor:* Any change occurring in odor of the core tablets due to coating process were noted prior to and after coating.

iii. *Weight variation:* Three series of ten coated tablets were each weighed before and after coating and the average weights calculated. The standard deviation and standard error values were calculated there from.

iv. *Hardness:* Ten enteric-coated tablets for each coating polymer were placed vertically in Schleuniger 4M apparatus and a vertical force was applied to each until the tablet broke and the value of force was recorded.

v. *Friability:* After the total weight of the tablets to be used was determined, coated tablets were placed in the drum of an Erwaka Friability Test Apparatus. The apparatus was run for 4 min at 25rpm. Subsequently, the tablets were brushed to remove any powder on their surface and then, reweighed. The difference between these two weight values and the pecentages were calculated.

v.Film thickness: Radius and height values of the tablets were measured using a micrometer before and after coating. The differences were used to calculate film thickness. The measurements were carried on for 3 series of 10 tablets.

vi.Disintegration: tests were performed in simulated gastric medium at 37±0.5°C for 2 hrs, according to USP XXIII (33). The tablets which were placed between two disc were then transferred into simulated intestinal medium. The temperature of the medium was kept at 37=0.5oC

vii. In vitro dissolution rates of tablets were investigated according to USP XXIII. Paddle method was applied. 900 ml of the phosphate buffered dissolution media, at different pH values (pH: 1, 2, 6.0, 6.4, 6.8) were prepared for each experiment. The temperature was kept at 37+ 0.5oC. 100 rpm stirring speed was applied and the samples were collected from the dissolution medium after, 5, 10, 15, 20, 30, 5, 60, 90, 120, 150, and 180 minutes. The dissolved amount of TNX was determined spectrophotometrically at 366 nm.

In vitro dissolution were apptied to 3 series of 6 tablets for each coating solution.

Results and Discussions

Assay of Tenoxicam Core Tablets:

TNX contents of core tablets obtained from a pharmaceutical company to coat with enteric-polymer were tabulated in Table 1.

Quality Control Tests (QCTs) performed on enteric-coated TNX-tablets

i. *Visual inspections*: Core tablets were yellow and oblongated, containing the logo of the manufacturing company on one surface.

ii. Odor: Core tablets did not exhibit any specific odor and undesired-smell formation did not occure due to coating.

iii. Determination of weight variation: The average weight values for core and coated tablets were tabulated in Table 2. Coating did not result with any significant weight increase. The values for average weight increase were in accordance with the values reported in the literature.

Table 1. Amount and percentage of tenoxicam (TNŞ) in core tablet (each claimed to contain 20 mg TNX) (n=3)

Tablets	Amount of TNX (mg) in each tablet	Percentage of TNX In each table
I	19.778	98.890
II	19.282	96.411
III	19.695	98.477
Mean	19.595	97.998
Standard Deviation (±)	0.22	1.1
Standard Error (±)	0.1	0.49

Table 2. Weight increases in tablets upon coating (n=3x10)

Number of tablets	Weight of core tablets (mg)	Weight of CAP coated tablets (mg)	Weight of CAT coated tablets (mg)	Weight of Aquateric coated tablets (mg)	Weight of Eudragit L-100 coated tablets (mg)
1	202.0	218.0	218.1	218.6	216.8
2	201.0	219.4	219.1	219.8	218.4
3	198.0	220.5	220.0	220.7	221.5
4	205.0	221.2	221.1	221.8	220.6
5	204.5	216.4	216.2	216.9	219.4
6	204.0	217.5	216.8	217.7	217.9
7	202.5	218.2	218.4	218.6	216.6
8	202.5	220.3	220.3	220.8	220.7
9	204.5	219.4	218.9	219.5	218.6
10	205.1	221.5	221.0	221.6	219.8
Mean	202.9	219.3	219.0	219.6	219.0
SD (±)	2.2	1.6	1.7	1.6	1.6
SD (±)	0.7	0.5	0.5	0.5	0.5
Average weight incease (%)	-	8.1	7.9	8.2	7.9
Suggested weight incease (%)	-	6-9	6-9	6-9	6-9

Table 3. Hardness values (kg) of core and coated tablets

Number of tablets	Core	CAP coated	CAT coated	Aquatericcoated	Eudragit-L-100-coated
1	2.5	4.7	4.3	3.2	3.7
2	1.9	4.6	4.9	3.2	4.2
3	2.5	4.9	5.2	2.7	3.7
4	2.5	5.3	4.8	3.2	3.9
5	1.9	3.9	4.1	2.8	4.2
Mean	2.3	4.7	4.7	3.0	3.9
SD (±)	0.3	0.4	0.4	0.2	0.2
SD (±)	0.1	0.2	0.2	0.1	0.1

iv.Hardness test values of core and coated tablets were given in Table 3. The data indicated that coating significantly increases the hardness, i.e. hardness values of the coated tablets were higher than those of the core tablets.

v.*Friability test:* No breaking or any other damage was observed upon application of the friability test on both core and coated tablets. Weight reduction due to friction was between the limits set in fiterature (O.5-1%). The data were tabulated in Table 4.

vi. Determination of film thickness: Radius and height values for core and coated tablets were tabulated in Table 5.

vii.Disintegration tests: Enteric-coated tablets did not disintegrate in the simulated gastric medium within 2 hours whereas CAP & CAT-coated & tablets disintegrated in the some medium within 10 and 12 minutes, respectively. Tablets coated with Aquateric and Eudragit L-100 disintegrated within 5 and 42 minutes respectively. All these data corresponded to the standards given USP XXIII.

viii. In vitro dissolution tests: As all the enteric-coated tablets did not exhibit any significant release at pH 1.2, all the dissolution experiments were conducted at pH values of 6.0, and 6.8. The dissolution profiles of core and coated tablets at these pH values were plotted (Figs 1-3).

Table 4. The data obtained from friability tests conducted on core and coated tablets (n=3)

Mean weight (mg) of tablets	Weight of tablets (mg)				
	Core	CAP coated	CAT coated	Aquateric coated	Eudragit L-100-coated
Prior to test	202.3	219.2	219.0	219.5	219.1
After the test	202.0	219.1	219.4	219.4	219.0
% Increase	0.148	0.046		0.046	0.046

Table 5. Radii and heights of core and coated tablets and film thickness of coated tablets (n=3)

Tablets	Core	CAP coated	CAT coated	Aquateric coated	Eudragit L-100-coated
Radius (mm)	11.7	11.9	11.8	12.0	11.9
Height (mm)	3.3	3.7	3.7	3.7	3.7
Film thickness (mm)	-	0.2	0.1	0.3	0.2
SD (±)	-	0.0004	0.0003	0.0007	0.0005

Approximately 99% of tenoxicam was released from core tablets in 120 minutes at pH 6.0 in 90 minutes at pH 6.4 and in 50 minutes at pH 6.8. This indicated that the drug substance might have been absorbed at duodeno-jejunal region.

The dissolution profiles of CAP, CAT, Aquateric and Eudragit L-100 coated tablets at pH 6.0 were lower than those obtained at pH 6.4 and 6.8. These were also in accordance with those given in the literature (33).

Among all the coating materials, Aquateric coated tablets gave the highest dissolution rates at all three pH values whereas Eudragit L-100 gave the lowest values. Thus, Aquateric was found to be the best agent for formulating enteric-coated tenoxicam tablets. The order of the coating polymers was as follows:

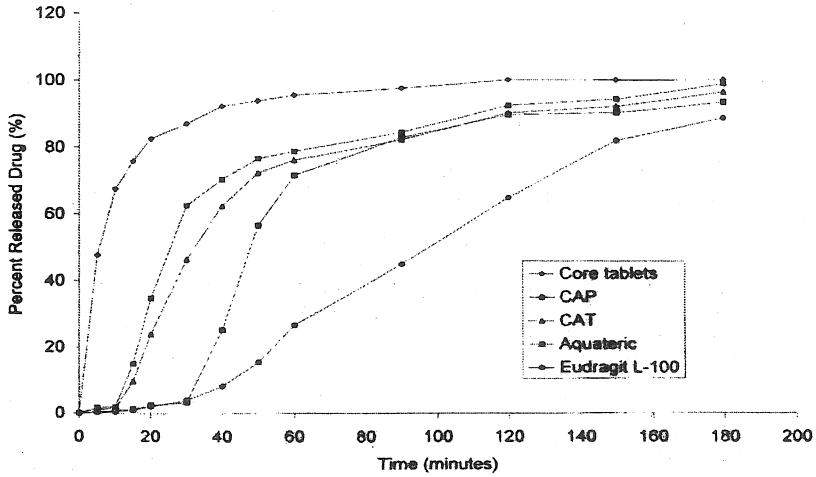

Fig. 1. Dissolution profiles of core and coated tablets at pH 6.0.

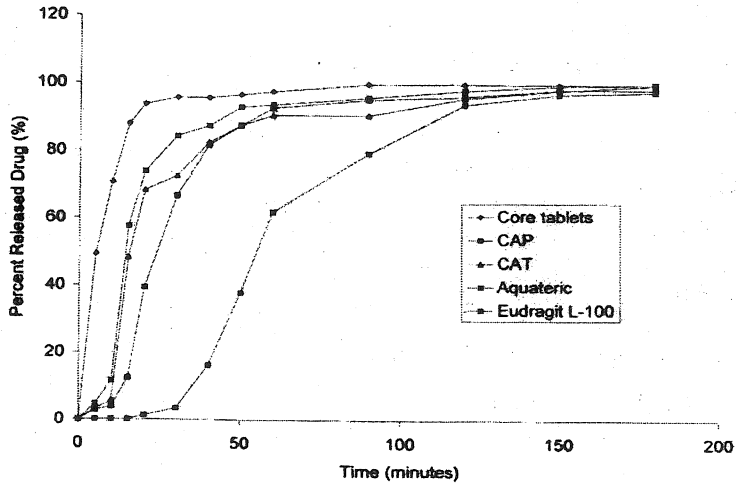

Fig. 2. Dissolution profile of core and coated tabmlets at pH 6.4.

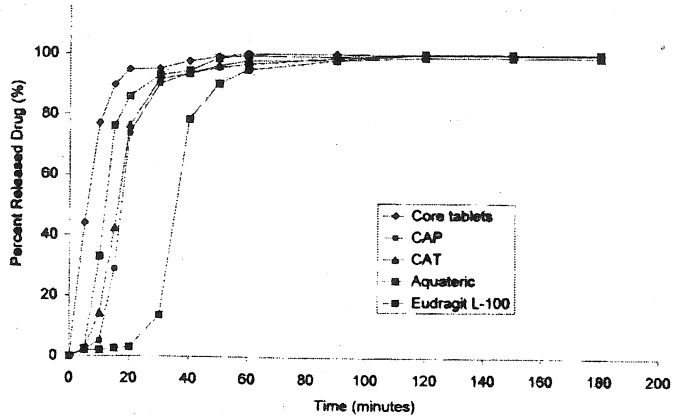

Fig. 3. Dissolution profiles of core and coated tablets at pH 6.8.

Aquateric >CAT>CAP>Eudragit L-100

In conclusion, gastric side effects of tenoxicam tablets may be overcome by employing film coating using Aquateric, CAT, CAP and Eudragit L-100. To support these *in vitro* data, an *in vivo* study was planned to be conducted by the authors.

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