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Original article

PREPARATION AND *IN VIVO* EVALUATION OF EUDRAGIT® L100/EUDRAGIT® NM 30D ENTERIC GRANULES CONTAINING DICLOFANAC SODIUM: ANTI-INFLAMMATORY AND ULCEROGENIC ACTIVITY

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Abstract

Extended-release granule formulations containing diclofenac sodium were prepared by wet granulation of Eudragit® L100 and Eudragit® NM 30D polymers. The drug release was examined in phosphate buffer (pH 6.8). The formulations allowed 100 % released drug by 720 min. The granules were evaluated with respect to their anti-inflammatory and ulcerogenic activity in rats. Eudragit® L100/Eudragit® NM 30D granules provide a significant and prolonged anti-inflammatory effect and also significantly reduce (52-74 %) the gastric lesion index.

Key words: *Eudragit L100, Eudragit NM 30D, Anti-inflammatory effect, Diclofenac sodium, Ulcerogenic activity.*

Diklofenak Sodyum İçeren Eudragit® L100/Eudragit® NM 30D Enterik Granüllerinin Hazırlanması ve *In vivo* Değerlendirilmesi: Anti-Enflamatuvar ve Ülserojenik Aktivite

Diklofenak sodyum içeren uzatılmış-salım sağlayan granül formülasyonlar, Eudragit® L100 ve Eudragit® NM 30D polimerlerinin yaş granülasyonu ile hazırlanmıştır. İlaç salımı fosfat tamponu (pH 6.8) içerisinde incelenmiştir. Formülasyonlar 720 dakikada % 100 salıma izin vermiştir. Granüller anti-enflamatuvar ve ülserojenik aktivite açısından sıçanlarda değerlendirilmiştir. Eudragit® L100/Eudragit® NM 30D granülleri anlamlı ve uzatılmış anti-enflamatuvar etki sağlamış ve aynı zamanda mide lezyon indeksini önemli derecede düşürmüştür (52-74 %).

Anahtar kelimeler: *Eudragit L100, Eudragit NM 30D, Anti-enflamatuvar etki, Diklofenak sodyum, Ülserojenik aktivite.*

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INTRODUCTION

Drug delivery technology is nowadays regularly used to improve the quality of pharmacotherapy. Targeted oral drug delivery may be a valuable approach when release of an active ingredient, because of its local action, in a certain segment of the gastro-intestinal tract and the reduction of gastrointestinal irritation (ulceration and bleeding) caused by drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) are needed or when release is desired after a certain lag-time (chronotherapy) (1-3). Therefore, enteric coatings using cellulosic polymers and methacrylic acid co-polymers such as, such as Eudragit L 100 as pH-dependent polymer soluble in intestinal fluid in pH 5.5 is widely used for the formulation of oral dosage forms and have been extensively studied (i.e. coating of tablets, matrix tablet, microspheres) (4-8).
NSAIDs are usually good candidates for the development of controlled release preparations, particularly through the oral route (9). NSAIDs are among the most widely used medications, but the side effects of these drugs frequently include gastrointestinal ulceration and bleeding (3). These compounds inhibit the cyclooxygenase enzymes (COX-1 and COX-2), which catalyze the conversion of arachidonic acid to prostaglandins (PGs) and thus prevent the formation of PGs. COX-1 is constitutive isoform and is found in the gastrointestinal tract, the kidney and platelets, and is believed to be responsible for the maintenance of physiological homeostasis such as gastrointestinal integrity and renal function (10).
The aim of the present work is to prepare and evaluate the suitability Eudragit® L100/Eudragit® NM 30D polymer blend for delayed release of NSAIDs. Diclofenac sodium was selected as the model drug in this study. Diclofenac sodium (DF-Na) is a phenylacetate non-steroidal anti-inflammatory agent synthesized by Ciba-Geigy of Switzerland in 1965 (11).
Diclofenac sodium is employed mainly in oral formulations, and the some extent, also for intramuscular injection and topical formulation (12). Diclofenac is commercially available as diclofenac sodium delayed-release (enteric-coated) tablets, diclofenac sodium sustained-release tablets, and as diclofenac sodium conventional tablets, diclofenac sodium gel formulation, diclofenac sodium injections (iv, im), diclofenac sodium suppositories and diclofenac sodium ophthalmic solution in Turkey (13). Its gastrointestinal side effects such as bleeding, ulceration are commonly seen. Eudragit® NM 30 D is a new matrix binder for sustained-release solid oral dosage forms. The polymer was used as a binder and as well as to extend the drug release. Eudragit® L100/Eudragit® NM 30D granules were prepared using wet granulation. The granules were characterized with respect to their in vitro release, anti-inflammatory and ulcerogenic activity in the rat.

EXPERIMENTAL

Materials

Diclofenac sodium was kindly provided by Deva Holding Inc. (Istanbul, Turkey). Eudragit® NM 30D and Eudragit® L100 were supplied by Rohm GmbH&Co. KG (Darmstadt, Germany). Carrageenan was purchased from Sigma (St. Louis, MO). Thiopental sodium was obtained from Ibrahim Ethem Ulugay A.S (Istanbul, Turkey).

Preparation of the granules

Granules were prepared by wet granulation using Eudragit® NM 30 D as a binder. This polymer is pH-independent polymethacrylate aqueous dispersion. It is not only an efficient matrix binder, but also exhibits good properties in wet granulation. Compositions of all blend formulations in this investigation were given in Table 1. Diclofenac sodium was mixed with Eudragit® L100. The powder masses were moistened with Eudragit® NM 30D and then, sieved

manually. The granules were dried for 24 hours at 40°C in a circulating air cabin. The granules were finally sieved again (2.38 mm mesh).

Table 1. Composition of granule formulations.

	Formulation	
	I	**II**
Blend ratio of Eudragit® L100:Eudragit® NM 30D (w/w)	0.5:1	0.5:1.5
Drug/polimer (w/w)	1:1.5	1:2

Thin layer chromatography

Stability test was performed using the TLC method (14,15). In brief, a pure diclofenac sodium was dissolved in ethanol (1 mL) by vortexing for 2 minutes. In parallel, formulation I and II were dissolved in 1 mL of ethanol by sonication for ten minutes and later centrifuged at 5000 rpm for 3 min for removing residue. These solutions were spotted on a silica coated TLC plate and was allowed to run with a mobile phase which was a mixture of toluene:formic acid:n-hexane (10:1.5:1). After development of chromatogram, the plate was taken out of the tank, dried and observed UV light. The developed spots were noted and the Rf values were measured. The diclofenac sodium stability was examined by means of comparison of the Rf values.

In vitro release studies

Since diclofenac is a weak acid (pKa=4), inherently has a negligible solubility in acid and detection of the released drug in acidic solution is not possible (16). Hence, the in vitro release of diclofenac sodium from the formulations was carried out by using USP XXIV rotating paddle method [900 mL phosphate buffer (PB; pH 6,8); 50 rpm; 37°C; n=3] (Sotax CH-4123, Switzerland) (17). Two milliliters of samples were taken at predetermined times and 2 mL of fresh medium (PB) was added after each sampling. Drug content was analysed using UV/Vis spectrophotometer ((ThermoSpectronic-HEλIOS β), at 280 nm. The analytical method was previously validated and verified for accuracy, precision and linearity. Standard solutions were prepared by diluting the stock solution (1000 µg/mL) with pH 6,8 phosphate buffer and linear response (y = 0,0408x - 0,0113; r > 0.999, n=6) was observed over the range of 2-20 µg/mL. Accuracy and precision was assessed using three replicates of three different concentration of diclofenac sodium (2, 8 and 20 µg/mL) on the same day (intra-day) and three consecutive days (inter-day). The values of intra-and inter-day accuracy and precision were given in Table 2.

Table 2. Precision and accuracy data of the developed spectrophotometric method for the analysis of diclofenac sodium.

		INTRA-DAY			**INTER-DAY**		
Method	**Added (µg /mL)**	**Found±SD**	**Precision % RSD**	**Accuracy**	**Found ± SD**	**Precision % RSD**	**Accuracy**
HPLC	2	1.940±0.022	1.11	-3.00	1.958±0,094	4.80	-2.08
	8	7.890±0.476	6.03	-1.38	7.639±0,177	2.33	-4.51
	20	19.770±0.565	2.86	-1.14	19.543±0,225	1.16	-2.29

SD : Standard deviation, RSD: Relative standard deviation , Accuracy : (% relative error) (found-added) / added x 100

Animal studies

In this study a total of 54 male Albino Wistar rats (200-240 g) which were obtained from Medical Experimental Research Centre, Atatürk University, were used. The animals were fed under normal conditions (22°C) in separate groups before the experiments. Animal experiments were carried out in an ethically proper way by following guidelines as set by the Ethical Committee of Ataturk University (B.30.2.ATA.0.23.85-111).

Effects of different diclofenac formulations on carrageenan-induced inflammatory paw edema in rats

Anti-inflammatory activity was evaluated using the well-known carrageenan induced rat paw oedema model of Winter et al. (18) using groups of six animals each. The anti-inflammatory effects of different diclofenac formulations on carrageenan-induced inflammatory paw oedema were studied on a total of 30 intact rats (18,19). Initially the rats were divided into 5 groups (n=6), 4 of which then received the aqueous suspensions of unloaded (drug free) Eudragit® L 100/Eudragit® NM 30 D granules, diclofenac sodium-loaded granule formulations (I and II; equivalent to 25 mg of diclofenac sodium/kg), and pure diclofenac sodium (25 mg/kg) respectively, by oral gavage. The control group received an equal volume of distilled water as vehicle. One hour after drug administration, 0.1 mL of 1% carrageenan was injected into the hind paw of each animal. Before carrageenan injection the normal paw volumes of the rats up to the knee joint were measured by plethysmometry. Carrageenan-induced increase in the paw volume (paw edema) was measured five times at 1 h intervals. The anti-inflammatory effects of the drugs were determined by comparing the results of the drug-treated groups with that of the control group. At the end of the experiments all rat groups were killed with a high dose of thiopental sodium (50 mg/kg).

The anti-inflammatory effect (AIE) was calculated using the following equation: AIE= (1- [(A-B)/(C-D)])*100, where A: mean paw volume of drug given group after carrageenan injection, B: mean paw volume of drug given group before carrageenan injection, C: mean paw volume of control group after carrageenan injection and D: mean paw volume of control group before carrageenan injection. The results are expressed as the mean±SD.

Determination of ulcerative effects of different diclofenac sodium formulations

The ulcerative activities of granules were investigated NSAID-induced ulcer model in rats (20). Animals were divided in four groups each containing six rats. The aqueous suspensions of the different granule formulations of diclofenac sodium (I and II), pure diclofenac sodium and unloaded Eudragit® L 100/Eudragit® NM 30 D granules were administered to 24-hour fasted rat groups by oral gavage. Six hours after drug administration, all rat groups were killed with a high dose of thiopental sodium (50 mg/kg). The stomachs of all the rats were excised. Ulcer areas on the surface of the stomachs were examined macroscopically and measured on square millimeter paper. The results obtained from the group received different formulations of diclofenac sodium and unloaded Eudragit® L 100/Eudragit® NM 30 D granules, have been evaluated by comparing them with that of pure diclofenac sodium group.

Statistical Analysis

One-way Anova was used in the statistical analysis of data. Tukey HSD test was employed as Post Hoc test and $p<0,05$ was considered significant.

RESULTS AND DISCUSSION

Eudragit® NM 30D is suitable polymer for wet granulation. EUDRAGIT® NM 30 D is a matrix binder for sustained-release solid oral dosage forms and also is very effective as a sustained release polymer. Eudragit® NM 30D based matrix systems show good storage stability (21, 22). The drug stability in the prepared granules was also tested by the TLC method. The Rf values of the diclofenac sodium in formulation I and II (0.49; 0,47, respectively) were compared with the Rf value of the pure diclofenac sodium (0.5) (Figure 1). Diclofenac sodium was detected and no other secondary spot was seen. These results confirm that Eudragit L100/Eudragit NM30D or the method of preparation has not affected the drug stability.

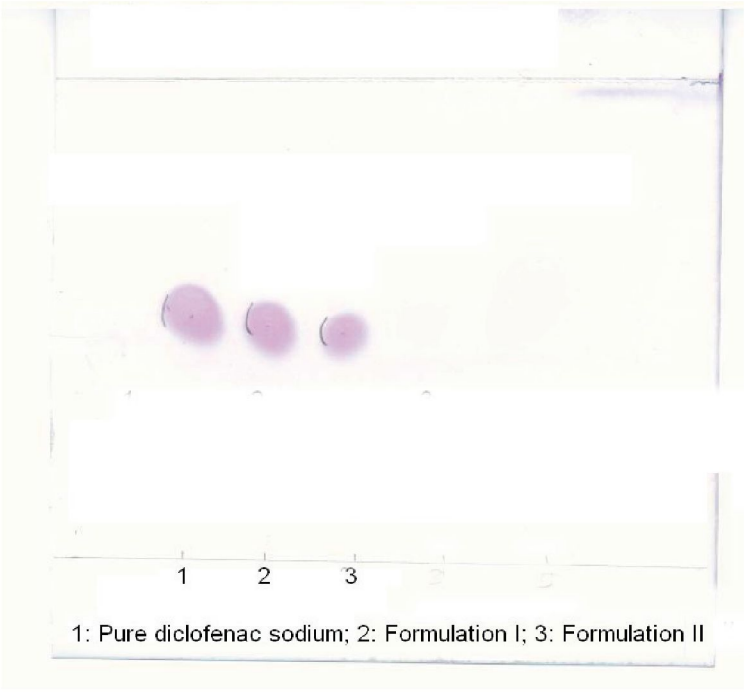

Figure 1. Thin-layer chromatography of pure DS and formulation I and II.

Fig. 2 displays the release profiles of diclofenac sodium from the granule formulations in sink conditions. In vitro release studies showed that around 100 % of the loaded drug was released into PB (pH 6.8) by 720 min. Combinations of Eudragit® L100 with Eudragit® NM 30D polymers were then selected to prepare granule formulations and investigated the influence of different polymer-polymer ratios (0.5:1 and 0.5:1.5 w:w) on the drug release (Table 1). Granules with higher content of pH-independent polymer exhibited a diffusional release profile, being the diffusion process prevailing over the erosion one. On the contrary, granules with a higher content of the pH-dependent polymer gave the highest percent of drug released at each time point, because, the erosion mechanism becomes predominant at intestinal pH (23). A mixture of Eudragit® L100 (pH-dependent) and Eudragit® NM 30D (pH-independent) polymers is sufficient to achieve a suitable release profile in a formulation. Qi et al. (24) prepared enteric-coated diclofenac sodium pellets compressed into tablets using Eudragit NE30D and Eudragit L30D-55. The drug release of the tablets was obtained as lower than 10% in 2 h in simulated gastric and 83% in 1 h in simulated enteric fluids. In another previous study, Eudragit S

microballoons were prepared for diclofenac sodium. A slow and controlled drug release of 60 to 84% was obtained over a period of 8 hours in simulated intestinal buffer. The authors reported that drug release was significantly affected by increased drug to polymer concentration at pH 6.8 (25). Moreover, El-Malah et al. examined the dissolution behavior of beads coated with the Eudragit® NE 30D and L 30D-55 blends (75:25; 80:20, respectively) (26). In this study, the 80:20 blend delayed drug release by approximately 7 h. Increasing Eudragit® NE 30D concentration in blend resulted in increasing release time.

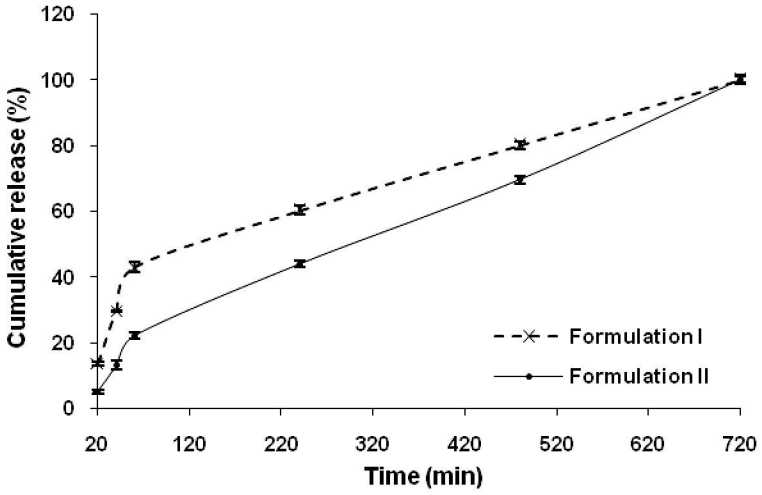

Figure 2. Release profiles of diclofenac sodium-loaded Eudragit® L100/Eudragit® NM 30 D granules (mean±SD; n=3).

Carrageenan-induced inflammation model is commonly used in determination of anti-inflammatory effect (18). It is known that carrageenan-induced inflammatory reaction has two phases: early and late phases. It was shown that while early phase is associated with release of histamine, serotonin and bradikynin, late phase is usually associated with prostaglandin release. It is known that cyclooxygenase and lipoxygenase enzymes have a role in carrageenan-induced inflammation formation (19). In our study, the significant reduction of rat paw oedema was observed by most of the granule formulations at 3 h and 5 h compared to control group (Table 3 and Figure 3, respectively). The anti-inflammatory activity of formulation I at doses of 25 mg/kg was shown by their ability to provide 62.29 % protection against carrageenan-induced rat paw oedema. On the other hand, the anti-inflammatory properties of formulation II at doses of 25 mg/kg was reflected by their ability to provide 49.88 % protection against carrageenan-induced rat paw edema. Formulation I has greater anti-inflammatory activity than formulation II, because, about 60 % and 44 % of diclofenac sodium from formulation I and II was released by 4 h, respectively as shown in Fig. 2.

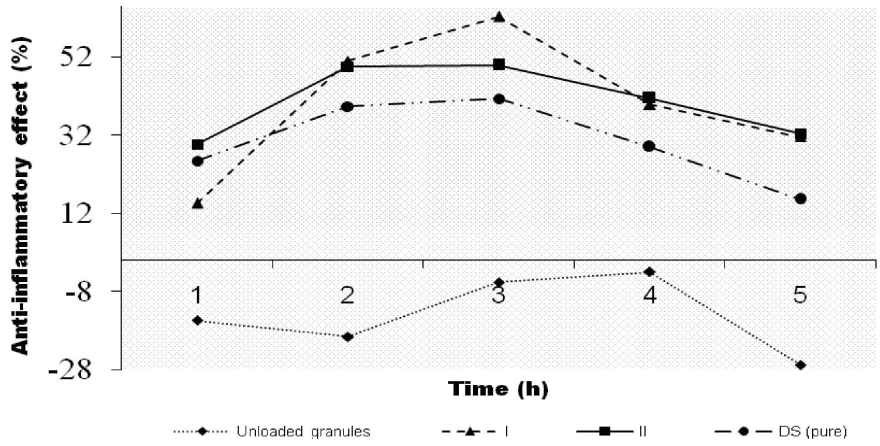

Figure 3. The anti-inflammatory activity of unloaded granules, pure diclofenac sodium as a control 25 mg/kg, formulation I and II equivalent to 25 mg of diclofenac sodium/kg on paw thickness following the paw inflammation induced by carrageenan injection.

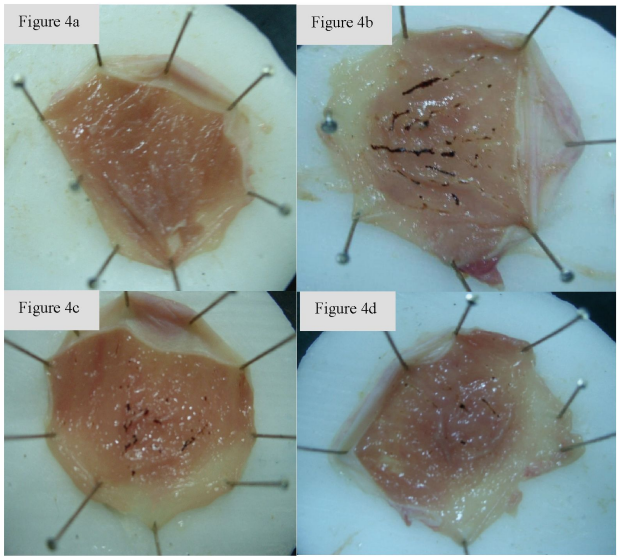

Figure 4. Macroscopic gastric damaged areas of unloaded granules (Figure 4a), pure diclofenac sodium as a control 25 mg/kg (Figure 4b), formulation I and II equivalent to 25 mg of diclofenac sodium/kg (Figure 4c and 4d, respectively).

Table 3. Anti-inflammatory effects of unloaded granules, formulations containing diclofenac sodium (I, II) and pure diclofenac sodium (DS) group at 3rd hour of carrageenan injection.

Drugs	Dose (mg/kg)	Number of animals	Paw volume of rats (mL)		Increase in inflammatory paw volume (mL) (mean±SD)	Anti-inflammatory effect %	p*
			Before inflammation (mean±SD)	At the 3rd hour of carrageenan injection (mean±SD)			
Unloaded granules	-	6	0.97±0.05	1.69±0.19	0.72±0.066	-5.60	>0.05
I	25	6	0.97±0.08	1.23±0.08	0.26±0.055	62.29	<0.0001
II	25	6	0.96±0.07	1.30±0.11	0.34±0.053	49.88	<0.01
DS (pure)	25	6	0.92±0.11	1.32±0.10	0.40±0.061	41.36	<0.005
Control	-	6	0.93±0.07	1.61±0.23	0.68±0.087	-	-

*p<0,05 was considered significant; SD : Standard deviation

Table 4. Ulcerative effects of unloaded granules, formulations containing diclofenac sodium (I, II) and pure diclofenac sodium (DS) group.

Drugs	Dose (mg/kg)	Number of animals	Ulcer area (mm^2) (mean±SD)	Ulcerative effect (%)	P
Unloaded granules	-	6	0.0±0.0	0	>0.0001
I	25	6	8.0±3.6	48	<0.02
II	25	6	4.33±1.2	26	<0.01
DS (pure)	25	6	16.67±3.1	100	-

SD : Standard deviation

The animals were fasted 24 h before the determination of ulcerative effects of the formulations. Fasting procedure may affect the development of inflammation, thus, different rat groups were used for examination of anti-inflammatory effects and ulcerative effects. Macroscopic analyses showed that there was ulcer formation in all stomachs applied the formulation I and II (equivalent to 25 mg of diclofenac sodium/kg), unloaded granule and in the control group given 25 mg/kg pure diclofenac sodium. In damaged stomachs, the lesions had been dispersed to stomach surface with different forms and sizes. There was remarkable hyperemia in the ulcerative stomachs. Hyperemia was more evident in the control group (given pure diclofenac sodium only) than in the others (given formulation I and II). As seen in Table 4, there was no ulcer formation in the rats that received unloaded granules (Figure 4a), the mean ulcer area was 16.67±3.1 mm^2 in the control group that received only pure diclofenac sodium (Figure 4b) and there was 8.0±3.6 mm^2 and 4.33±1.2 mm^2 ulcer area in the stomachs of the formulation I and II groups, respectively (Figure 4c and 4d).

CONCLUSION

The drug release behavior was markedly influenced by the kind of Eudragit used, and, when utilized in mixtures, by their relative w/w ratio. Appropriate combinations of a pH-dependent polymer (Eudragit® L100) with a pH-independent one (Eudragit® NM 30D) were suitable for sustaining diclofenac sodium release. The use of granules of Eudragit® L100/Eudragit® NM 30D blend provide a significant and prolonged anti-inflammatory effect and also significantly reduce the gastric lesion index.

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