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Effect of NSAIDs on thermomechanical properties and permeability of Eudragit RS free films

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ABSTRACT

The purpose of the present study was to investigate the influence of ibuprofen, indomethacin, diclofenac and naproxen for sustained release drug delivery systems, on the thermal and mechanical properties of polymeric free films of Eudragit RS. Free films with different drug contents were prepared by casting-solvent evaporation method. Thermal properties of free films were determined using a differential scanning calorimeter. Morphology of films, mechanical tests and water vapor transmission were also studied. Overall results demonstrated that percent elongation and elasticity of ERS films was increased by incorporation of ibuprofen and indomethacin in the films. Plasticization effect of ibuprofen was mainly due to lipophilic interaction of drug and polymer backbone while in the case of indomethacin, separation of polymeric chains via drug crystallization between polymer segments could affect the elasticity of free films. Naproxen and diclofenac not only had no plasticizing effect but also decrease the flexibility of polymeric films.

Keywords: Plasticization, Eudragit RS, NSAIDs, Free film.

INTRODUCTION

The evaluation of the physicomechanical properties of coating films is completely necessary due to widely use of these materials. Polymeric materials have been used to coat pharmaceutical solid dosage forms for protective and functional purposes [1]. Drug delivery systems based on polymethacrylates have been focused in the last decades. Eudragit RS PO is one of these materials which have time-dependent characteristics and have been used in matrix polymeric systems [2] as well as coating for drug delivery formulations [3,4].

Many pharmaceutical polymers exhibit brittle properties and require addition of a plasticizing agent to obtain an effective coating. Plasticizers do their function by weakening the intermolecular attractions between the polymer chains and generally decrease the tensile strength and the glass transition temperature and increase the flexibility of the films [5]. Plasticizers are

necessary components to reduce brittleness, improve flow, impart flexibility, and to increase toughness, strength, and tear resistance of the film [6]. Plasticizers used in polymeric systems should be miscible with the polymer and exhibit little tendency for migration, exudation, evaporation, or volatilization. Many compounds can be used to plasticize polymers, including water, phthalate esters, sebacate esters and citrate. Various glycol derivatives including propylene glycol, polyethylene glycol and vegetable oils have also been used to plasticize polymeric films [7,8].

The effectiveness of a plasticizing agent is dependent, to a large extent, on the amount of plasticizer added to the polymeric system and the extent of polymer-plasticizer interaction. The degree of plasticizer-polymer interactions has been extensively characterized using differential scanning calorimetry and the decrease in the glass transition temperature of the polymer with the addition of a plasticizing agent is a common measure of plasticizer effectiveness [9,10].

The selection of a plasticizer for a polymeric drug delivery system is very important in the development and optimization of a controlled pharmaceutical solid dosage form. Limitations should be considered for efficiency and compatibility of different types of plasticizers [11]. Moreover, there have been some reports about potentially interaction between plasticizer and drug which could influence drug release through a polymeric film [12,13]. Therefore, plasticization with non-traditional plasticizers can be more valuable due to reducing interactions and increased compatibility. Of these, materials such as surfactants [14], preservatives [15] and even drugs [8,11,16] have been attempted as plasticizing agents.

In previous studies about the plasticizing effect of drugs on polymethacrylates it was showed that ionic interaction between anionic groups of drugs such as ibuprofen and cationic quaternary ammonium groups of Eudragit RS is the main mechanism of increased flexibility of polymer film [8,17]. On the other hand, different mechanisms of plasticization act of drugs have also been theorized in resources [11,18]. In the current study, four frequently used NSAIDs including ibuprofen, indomethacin, diclofenac and naproxen were investigated for their influence on the thermal and mechanical properties of polymeric films of polymethacrylates. These drugs have the same anionic carboxylic acid group in their chemical structure and differ by their hydrophilic character. Also, potentially using of the non steroidal anti inflammatory drugs (NSAIDs) in the enteric coated system arise from their side effects can candidate them for evaluating plasticizing effect of drugs. Eudragit® RS PO (ERS) was selected from polymethacrylates since this polymer possesses quaternary ammonium group which could potentially increase the possibility of ionic interaction between drug and polymer. Therefore, the plasticizing effect of different drugs as well as the mechanism of plasticization could be more deliberating.

MATERIALS AND METHODS

Materials

Eudragit RS PO (ERS) (Rohm Pharma, Germany), tributyl citrate (Morflex, USA), ibuprofen (Hakim, Iran), indomethacin (Hakim, Iran), diclofenac (Hakim, Iran), Napoxen (Zambon, Swittzerland), magnesium nitrate hexahydrate (Aldrich, Germany), Calcium chloride (Merck, Germany) were obtained from indicated sources. All chemicals were of analytical and pharmaceutical grade.

Preparation of free films

A 10% (w/v) solution of ERS was prepared by dissolving powder of polymer in isopropyl alcohol:distilled water (9:1 ratio). Then, a fixed amount of tributyl citrate (10% of total polymer

content) or drug was added (10, 20 and 30% w/w Based on the dried polymer mass). Sufficient time must be allowed for plasticizer uptake into the polymer phase before drying. The resulted solutions were transferred to teflon plates (10×10 cm). Then films were dried in an oven at 40 °C for 24 h. After that, plates were transferred to a desiccator with 100% relative humidity (RH) for 24 h. The films were then cut with a scalpel to different special pieces for various tests. The thickness of the films was measured at five different places using a micrometer (Käfer, Germany) and the average thickness of 180-250 μm was selected. Free films were stored in a desiccator with 50% RH resulted by a saturated solution of magnesium nitrate hexahydrate at room temperature for future tests.

Water vapor transmission test

Water vapor transmission (WVT) of free films was determined in triplicate. The diameter of water vapor transmission cell was 3.5 cm. Then it filled with 10 ml of distilled water to produce 100% RH. The cell is sealed with the polymeric film. Rubber rings followed by a metal ring are often used to prevent water vapor egress through any areas other than the film. Another piece of the same free film fixed on another cell without water as reference. Both sample and reference were accurately weighed (±0.0001 g) and placed in a desiccator containing calcium chloride($CaCl_2$) as a desiccant and filled with silicagel (0% RH) and weighed periodically over a specified time period (24, 48, 72, 96,120 h). The profile of mass change was plotted versus time for each sample. Water vapor transmission (WVT) was calculated using following equation:

$$WVT = \frac{wx}{tAP0(RH2-RH1)}$$

where w/t is the mass change (flux, mg/h) resulted from slope of profile of the mass change versus time, x the film thickness (mm), A the area of the film surface exposed to the permeant (m^2), P_0 the vapor pressure of pure water (kPa), and ($RH_2 - RH_1$) is the relative humidity gradient. At 25 °C, P_0 is 3.159 kPa [19].

Thermal analysis of free films

The thermal properties of polymer, drugs, their physical mixtures and free films were determined using a differential scanning calorimeter (Mettler-Toledo, Switzerland). 10 mg samples were accurately weighed in aluminium crucibles and then sealed and pierced. Samples were subjected to the thermal program (0-290°C heating range; heating rate 10°C/min), under a nitrogen flow, in parallel with an empty crucible as a reference.

Scanning electron microscopy

Scanning electron microscopy was used to study the morphology of the polymeric free films. Samples were coated with silver for 60 seconds under an argon atmosphere using a Polaron Ronge sputter coater in a high-vacuum evaporator. Scanning electron microscopy was performed using a scanning electron microscope (Leo 1455 VP) at 25 kV.

Calculation of log D and drug lipophilicity

Log D parameter was calculated for all experimented drugs as a valuable determinant of drug lipophilic character. The Software MarvinSketch 5.2.1-1 was used for calculation of log D.

Mechanical properties of free films

The mechanical properties of the free films containing different drugs and tributyl citrate were evaluated using Universal testing machine (Model WDW, REP, China) fitted with a 5 kN load

cell. The initial distance between two grips (initial length of the film specimens) was 30 mm and the speed of grip separation was set at 10 mm/min. The extension-force graphs and percent elongation (or percent strain at break) were obtained with a computer system attached to the apparatus. The experiment was repeated 5 times for each formulation and the mean value was reported.

Statistical analysis of data

One-way analysis of variance was used to assess the significance of the differences among different groups. Student, Newman, Keuls post-test was used to compare the means of different treatment groups. Results with $p<0.05$ were considered to be statistically significant.

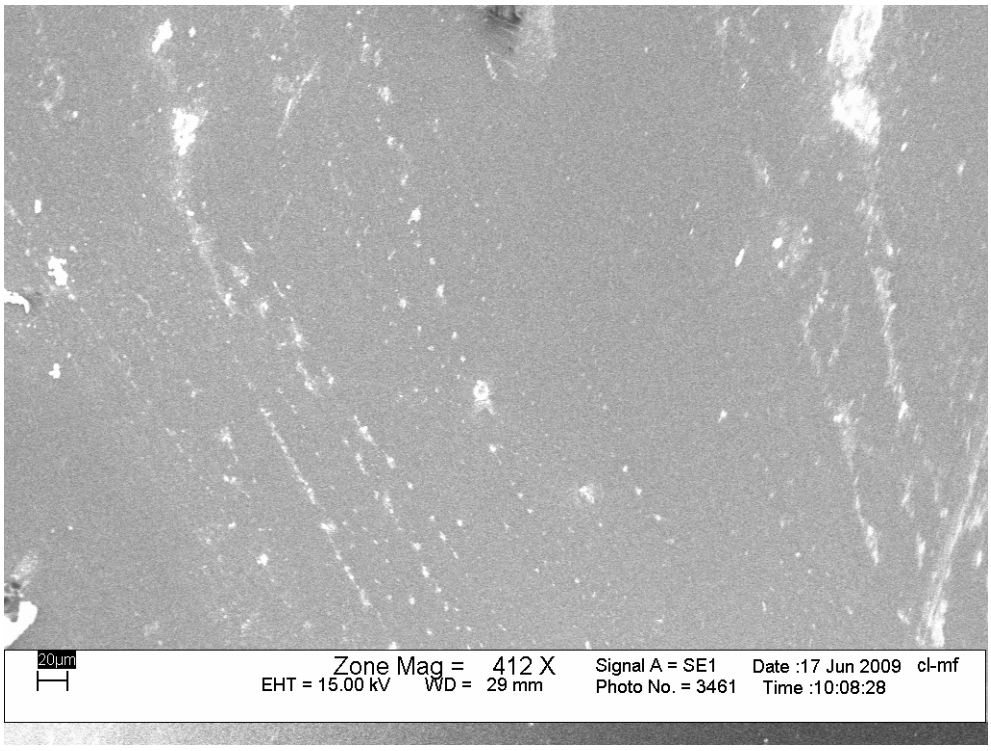
Results and discussion

The results of mechanical tests on ERS free films are shown in Table 1. The percentage elongation of the 10% ibuprofen loaded films was the same as films containing 10% tributyl citrate and significantly increased as the ibuprofen concentration in the film increased from 10 to 30%. In contrast, the tensile strength of free films was decreased by inclusion of ibuprofen so that 30% ibuprofen loaded films had no measurable tensile strength. The results for free films containing ibuprofen demonstrated that increasing ibuprofen content in films led to increase their percentage elongation due to drug plasticizing effect. Addition of a plasticizer usually enhances the flexibility and elongation of a film, while film tensile strength is generally reduced [20,21]. The SEM images of free films containing ibuprofen showed soft and smooth surface that confirms the plasticizing effect of drug (figure 1). Wu and McGinity had shown that ibuprofen acts as an effective plasticizer for films prepared from Eudragit RS aqueous dispersions. They suggested that disordered placement of the polymeric chains due to disruption of chains interaction could result a highly amorph structure and reduce the rigidity and brittleness of polymeric film [17]. In our study, thermal studies performed by DSC demonstrated that ERS and ibuprofen have impressed on their thermal properties. In physical mixture of ERS and ibuprofen both the melting peak of drug and Tg of polymer shifted to lower temperatures (figure 2); While in the case of free films Tg of polymer is disappeared and peak of ibuprofen melting point changed to a broad peak. As a matter of fact, the influence of ibuprofen on reduction of Tg of polymer suggested that drug loading would increase polymer chain movement and elasticity. Glaessl et al. demonstrated that drugs could act as plasticizer of eudragits mainly by two different mechanisms; an ionic interaction between anionic groups of drug and quaternary ammonium groups of polymethacrylates, and drug-polymer interactions via polymer backbone independent of the ionic links [18]. The second mechanism could be enhanced by substituting more lipophilic drugs in the polymer chains. Table 2 summarized the lipophilicity of different types of NSAIDs used in current investigation. As shown, ibuprofen exhibited the highest level of log D as a key parameter reflecting lipophilic character of a chemical. Therefore, the drug molecules can diffuse between polymeric chains and interact with polymer which enhances chain movement and the resulted plasticizing effect. The results of WVT (Table 3) confirmed this claim and it was observed that WVT of ibuprofen-loaded free films in different drug concentrations was least compared to the other free films and therefore, free films containing ibuprofen were more lipophilic. As a consequence, more hydrophobic nature of ibuprofen was the main mechanism of plasticizing effect of drug rather than ionic interaction between anionic group of drug and cationic side chains of ERS.

Free films containing 10% of indomethacin did not show significant plasticizing effect but by increasing amount of drug from 10 to 30% an increase in elongation and decrease in tensile strength could be seen (Table 1) so that percent elongation of films containing 30% of indomethacin was equal with 30% ibuprofen-loaded films ($p>0.05$). SEM images of

indomethacin-loaded ERS free films showed a rough and uneven surface with the presence of tiny crystals which may be related to recrystallization of drug during free film preparation (figure 3). Actually, standing the drug crystals between polymeric chains diminished the integrity of polymer and therefore at higher concentrations of indomethacin, drug lowered the tensile strength of free film and induced the plasticizing effect (Table 1). Enhancing the flexibility of films via crystallization of drug between polymeric chains could be explained by another research in which crystallization of guaifenesin in the polyethylene oxide free film reduced the tensile strength of film through disrupting hydrogen bonds between polymer fragments [16]. The data of WVT for indomethacin-loaded films showed that water vapor transmission was increased with high drug levels, so that free films containing 30% indomethacin exhibited the maximum WVT (Table 3). Thus, it can be concluded that incorporation of drug crystals between ERS polymer chains allows separation of polymeric links which leads to more facile water vapor permeation. On the other hand, the higher amounts of WVT of films loaded with indomethacin compared to ibuprofen-loaded films could be due to the more hydrophilic nature of indomethacin as revealed by results of log D of both drugs (Table 2). DSC thermograms did not show significant changes in thermal properties of ERS and indomethacin (data not shown) which can confirm the lack of possible effect of drug on crystallinity of polymer.

Figure 1. Scanning electron micrographs of surface of the ERS free film containing 30% ibuprofen



The mechanical tests of ERS and diclofenac free films exhibited a decrease in elasticity upon addition of drug. Increase in drug level from 10% to 30% led to increase in tensile strength of free films. Actually, despite the fact that hydrophobic character of diclofenac (Table 2) might raise the lipophilic interaction between drug and polymer it was shown that films containing 30% diclofenac had the minimum percent elongation compared to the films with the same level of ibuprofen and indomethacin. The effect of diclofenac/ERS ratio on the plasticization of free films was demonstrated in another investigation in which it was shown that the strength of possible interaction between the ionic groups of drug and polymer and the plasticizing effect of

drug is dependent to the drug/polymer ratio [22]. In our study it was seen that increase in drug level could decrease elasticity of ERS films. Furthermore, SEM photographs of diclofenac-loaded films showed the existence of cracks on film surface (figure 4) revealing the brittleness of the films.

Figure 2. DSC thermograms of ERS, ibuprofen, their physical mixture and free films

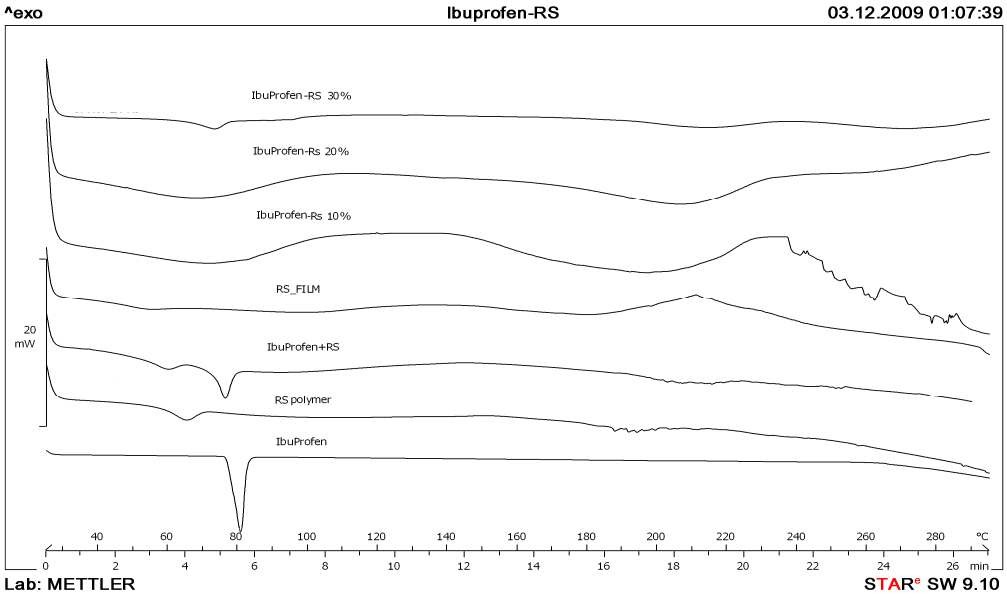


Figure 3. Scanning electron micrographs of surface of the ERS free film containing 30% indomethacin

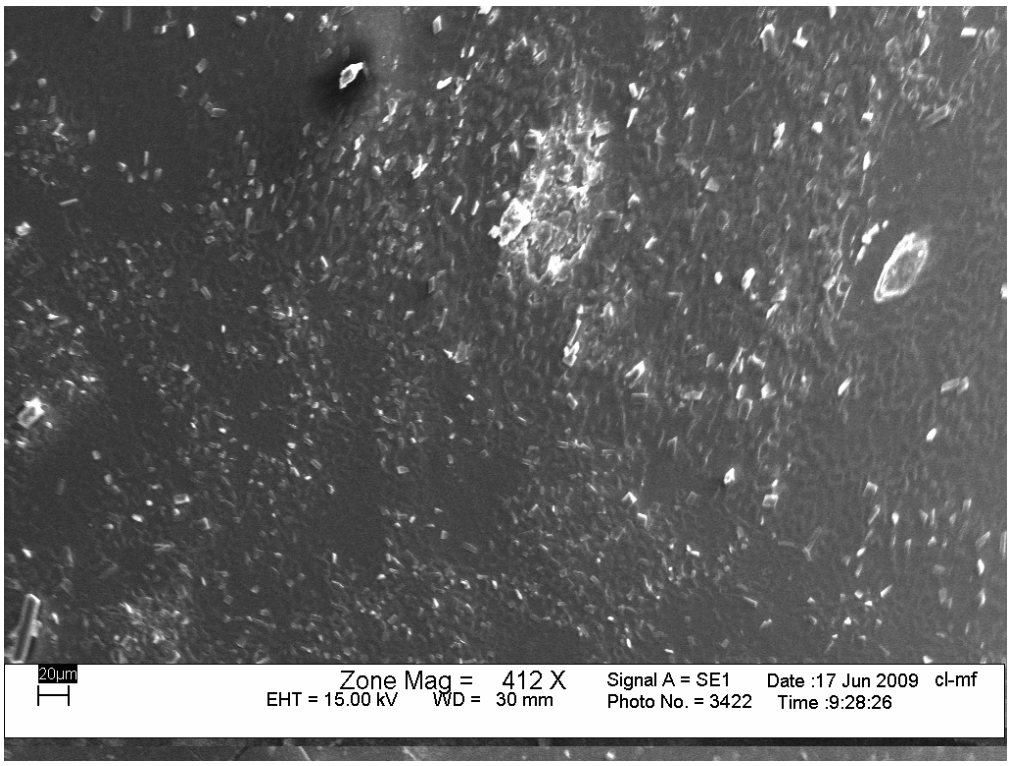


Figure 4. Scanning electron micrographs of surface of the ERS free film containing 30% diclofenac

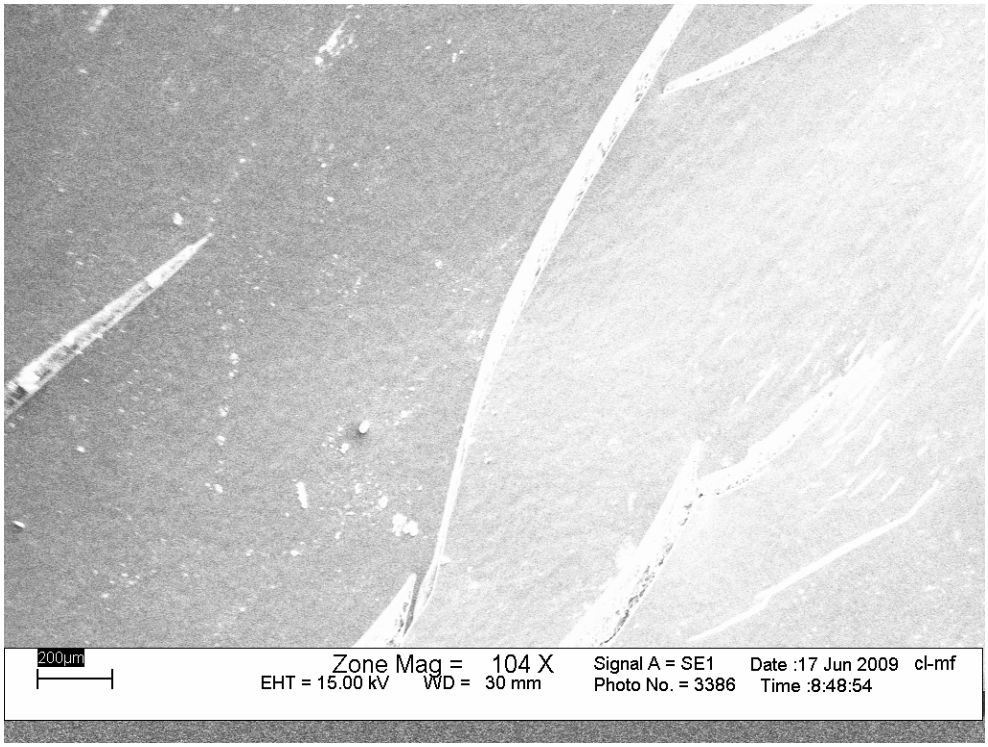


Figure 5. DSC thermograms of ERS, naproxen, their physical mixture and free films

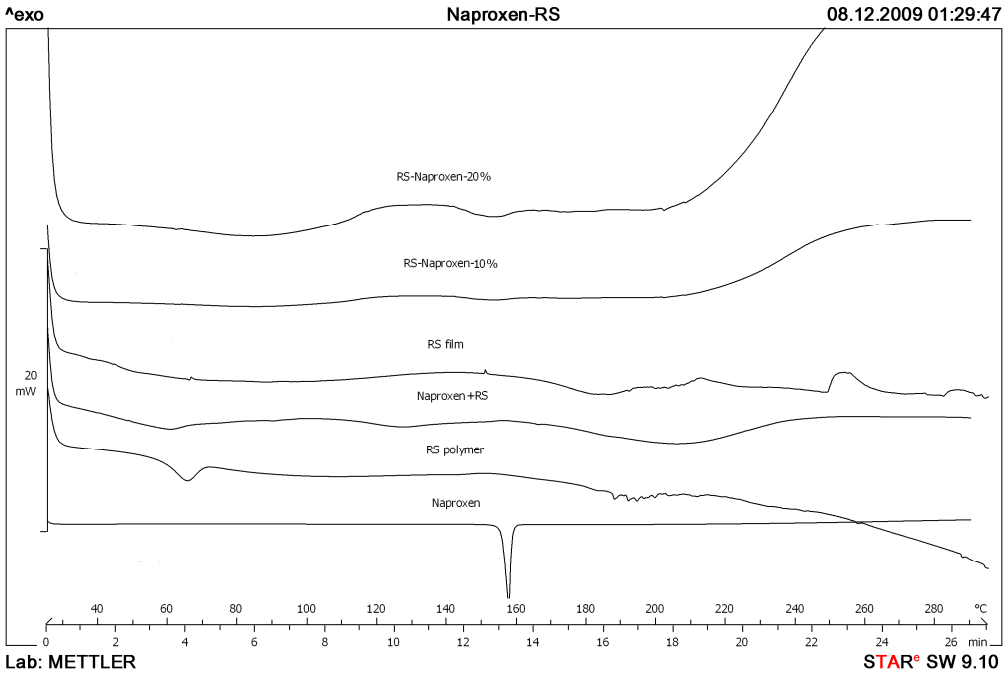


Table 1. Results of mechanical tests of ERS free films containing different drugs

Drug	Drug content	Tensile strength (N/mm^2)	Percent elongation
Ibuprofen	10%	3.505±1.215	330.949±82.290
	20%	1.111±0.124	519.383±5.254
	30%	0.000	686.790±101.564
Indomethacin	10%	4±0.253	100.050±20.543
	20%	3.171±0.274	363.523±56.936
	30%	0.790±0.274	540.077±48.766
Diclofenac	10%	3.027±1.049	103.498±24.838
	20%	2.660±0.274	122.488±29.960
	30%	7.240±1.810	62.743±5.561
Naproxen	10%	5.330±0.577	213.7±47.846
	20%	6.136±1.992	188.506±29.802
	30%	ND	ND
Tributyl citrate	10%	2.455±0.215	236.474±48.894

Table 2. Calculated log D for different experimented drugs

Drug	Log D at ERS solution with pH 6.5
Naproxen	0.70
Diclofenac	1.79
Indomethacin	0.89
Ibuprofen	2.19

Table 3. Results of WVT tests of ES and ERS free films containing different drugs

Drug	Dug content	Mass change (mg/h)	WVT(Mean±S.D.; n=3) (mg mm/m^2hkPa)
Ibuprofen	10%	1.833	1.149± 0.488
	20%	2.03	1.205±0.583
	30%	2.942	1.941± 0.421
Indomethacin	10%	3.631	2.396± 0.976
	20%	4.59	3.332±1.034
	30%	9.504	6.586± 1.030
Diclofenac	10%	3.392	2.462±0.805
	20%	5.54	3.839±1.247
	30%	4.120	3.127± 0.991
Naproxene	10%	7.375	4.867±1.373
	20%	7.132	4.472±1.237
	30%	-------	-------
Tributyl citrate	10%	3.652	2.290±0. 502

CONCLUSION

Results of this study showed that physicomechanical and permeability characteristics of ERS polymer can be affected by addition of some NSAIDs and more consideration is needed during development, preparation and shelf life of controlled release polymeric systems containing these drugs. Addition of ibuprofen and indomethacin could increase the elasticity of ERS films by different mechanisms and decrease their tensile strength in compare with classic plasticizer, while naproxen and diclofenac not only had no plasticizing effect but also lowered the elasticity of polymeric films.

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