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Original article

PHYSICAL PROPERTIES AND *IN VITRO* RELEASE STUDIES ON SOTALOL MONOLITHIC FILMS PREPARED BY EUDRAGIT POLYMERS

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Abstract

The objective of this study is to investigate physical characteristics of monolithic films and in vitro release of sotalol, prepared by either Eudragit E100 (E100) or Eudragit RL100 (RL100) combined in a ratio of 50 % w/w with Eudragit NE40D (NE40D). Films including 3 % w/w sotalol of dry polymer weight were prepared from methanol:acetone solvent mixture moulded onto a PVA backing membrane. The pore former effect of adipic acid or citric acid monohydrate (1.5 % w/w and 5% w/w) was evaluated on the E100:NE40D film in order to modify the release of sotalol. Uniformity of films was evidenced by low standard deviations of thickness and drug amount studies as well as high sotalol contents. The in vitro release studies carried out by vertical Franz cells. Films formulated with RL100 polymer gave higher degrees of swelling accompanied with higher in vitr o release rates of drug that could attributed to the higher permeability of this polymer. The existence of organic acids inside of films affected the release profiles and acid pKa value with low aqueous solubility of adipic acid caused a rapid release of drug rather than citric acid. Morphological analysis of acid containing films performed by scanning electron microscopy supported the drug release data. Obtained kinetic data from in vitro dissolution profiles indicated that drug release governed by diffusion mechanism.

Key words: *Sotalol, Eudragit, Monolithic film, Pore formers, Swelling.*

Eudragit Polimerleri ile Hazırlanan Tek Tabakalı Sotalol Filmlerinin Fiziksel Özellikleri ve *In vitro* Salım Çalışmaları

Bu çalışmanın amacı Eudragit E100 (E100) veya Eudragit RL100 (RL100) ile %50 a/a oranında Eudragit NE40D (NE40D) kombine edilerek hazırlanan tek tabakalı filmlerin fiziksel özellikleri ve in vitro sotalol salımının incelenmesidir. %3 a/a kuru polimer ağırlığında sotalol içeren filmler metanol:aseton çözücü karışımı içersinde PVA sırt materyaline dökülerek hazırlanmıştır. Sotalol salımını modifiye etmek amacıyla adipik asit veya tek sulu sitrik asitin (%1.5 ve %5 a/a) por oluşturucu etkisi, E100:NE40D film üzerinde incelenmiştir. Filmlerin homojenliği, kalınlık ve etkin madde miktar tayini sonuçlarına ait standart sapma değerlerinin küçük ve miktar tayini sonuçlarının yüksek oluşu ile kanıtlanmıştır. In vitro salım çalışmaları dikey Franz hücreleri ile yapılmıştır. RL100 ile formüle edilen filmler, polimerin yüksek geçirgenliğe sahip olmasına bağlanabilen, yüksek şişme değerleri ile birlikte daha hızlı salım göstermişlerdir. Filmlerdeki organik asitlerin varlığı salım profilini etkilemiş ve adipik asidin, sulu ortamdaki düşük çözünürlüğü ile asit pKa değeri, filmlerin sitrik asitle olduğundan daha hızlı etkin madde salmasına neden olmuştur. Asit içeren filmlerin taramalı elektron mikroskobu ile yapılan morfolojik analizleri etkin madde salım verilerini desteklemiştir. In vitro çözünme hızı profillerinden elde edilen kinetic veriler etkin madde salımın difüzyon mekanizmasıyla gerçekleştiğini göstermiştir.

Anahtar kelimeler: *Sotalol, Eudragit, Tek tabakalı film, Por oluşturucu, Şişme.*

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INTRODUCTION

Sotalol a non-selective beta-adrenergic receptor blocking agent is used for supraventricular and ventricular arrhythmias in adults and children. Oral delivery of sotalol can probably cause proarrhythmic effects related inadequate dosing that ends one of important side effect torsades de pointes especially seen in pediatric patients (1). Hence, achieving an adequate dosing of sotalol in a sustained manner, transdermal way can be a solution to prevent or reduce mentioned side effects (2-4).

Transdermal patches are innovative drug delivery systems used for bypassing hepatic first-pass metabolism and increasing the fraction absorbed. This maybe accompanied by the reduced dosing frequency required for a chronic treatment and thus, improved compliance (5). As a kind of patch, monolithic transdermal systems are favourable due to their ease of fabrication and lack of dose dumping (2,6-10). Several authors have reported the use of polymethacrylate kinds of polymers in matrix formulations for monolithic transdermal systems generally prepared by casting and drying drug-polymer organic solutions or suspensions. Most preferable commercial polymethacrylate polymers are Eudragits having high capacity for incorporating drugs and skin toleration (3-4,11-17). Especially Eudragit E100 having a poor swelling capacity because of lack of quaternary ammonium groups (QAGs) and Eudragit RL100 freely permeable to water and has a high swelling capacity have often used in preparation of monolithic systems (15,18). Some studies has reported that Eudragit polymers which are nontoxic, non-absorbable and stable in their film forming properties could provide modified release of drugs from monolithic films (4,15).

The objective of this study was to investigate the sotalol release from Eudragit based transdermal monolithic films that would evaluate by physical properties and drug release governed by the type of polymers and pore formers.

EXPERIMENTAL

Materials

Sotalol (Adeka Drug Comp. Samsun/Turkey), Eudragit (E100, RL100 and NE40D) polymers (Evonik Röhm GmbH, Darmstadt/Germany), adipic acid (AA), citric acid monohydrate (CA), dibutyl sebacate (DBS) (Sigma), polyvinyl alcohol M_W 72000 (PVA) (Sigma), HEPES (Fluka), cellulose acetate membrane (0.22 μm, Sartorius) were used in the studies.

Preparation of films

Polymer films were prepared by solvent casting method with methanol:acetone (1:1, v/v) in glass moulds 22.89 cm^2 in area (19). The glass moulds inside were covered with 0.095 mm PVA as backing membrane by casting from 5 % w/w aqueous solution of PVA at 70 °C (10). Sotalol (3 % w/w of dry polymer weight) was dissolved in methanol, later on polymer(s) and DBS (20 % w/w of dry polymer weight) were added to the beaker. The mixture was dissolved by adding acetone and stirring for 60 min at 500 rpm. Film solution was poured onto a PVA covered glass mould and cast on PVA membrane following by evaporation at 50 % relative humidity and 25 °C conditions for 5 days before the experiments (19). Drug content of films was calculated by considering the area of glass moulds. The compositions of films were given in Table 1. Each formulation was prepared as three different moulds (batches) to obtain three parallels.

Investigation of film properties

Initially, film preparation method was validated by standardization of thickness and drug amount in films, which were given in Table 2. These studies were carried out on three batches for each formulation and repeated three times from the each batch, thus all the experiments (thickness, swelling and *in vitro* release) were performed by nine parallels for each formulation. Drug and excipient free films were set off from the method given in Röhm Pharma Catalogue (20) and were predicted as 0.300 mm in thickness. Sotalol contents of films were calculated as 0.9 mg/cm^2 theoretically.

Thicknesses and Drug Amounts of Films

Thickness of films were determined by using a micrometer (NSK, Japan) obtained from three batches and three discs for each batch (n=9) which were cut from different sides of the glass moulds with a circular metallic die of 1.1 cm in diameter (21) and the thicknesses were given as mm ± SD in Table 2. In order to determine drug amounts and uniformity in glass moulds, sotalol quantitated from these discs by using spectrophotometer at 229 nm (Shimadzu 1404, Japan) after shaking continuously for 48 hours in 25 ml of HEPES buffer (pH 7.4) and ultrasonicating for 1 hour (4). Sotalol content of films was calculated as mg/cm^2 ± SD for each disc (Table 2).

Swelling Studies

Swelling studies were carried out by drying the pieces of 1 cm^2 film in an oven at 50 °C for 24 h and then dried film was accurately weighed and immersed in a flask containing dissolution media (HEPES buffer, pH 7.4) at 37± 0.5 °C. The swollen sample was withdrawn from the medium at the end of 1, 8 and 24 hours. After removal of excess surface water of disc with a filter paper, sample was weighed and percentage swelling I_s (%), was calculated as follows;

$$I_s\ (\%) = (W_s - W_d) / (W_d) \times 100$$

Where W_d is weight of dried polymer film and W_s denotes the weight after swelling (21, 22). Also, the change in thickness (%) was evaluated in same manner in order to explain swelling phenomenon. The results were given in Table 2 and Fig.1.

In vitro release studies

In vitro drug release studies were carried out using jacketed vertical Franz diffusion cells with a surface area of 2.2 cm^2 and a receptor compartment capacity of 20 mL. Discs containing 0.9 mg sotalol were cut from the formulated films and settled between the chambers of diffusion cells on a 0.22 µm cellulose acetate membrane as a donor phase. Subsequently wetted with 0.1 mL of 100 mM, pH 7.4 HEPES buffer in order to ensure humidity (21,23). The whole assembly was continuously stirred at 500 rpm and the temperature was maintained at 37 ± 0.5 °C. Samples were withdrawn at predetermined time points (0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8 h) during 8 hours and receptor phase was replenished by adding 0.5 mL of fresh buffer. Collected samples were filtered and then analyzed spectrophotometrically (Shimadzu 1404, Japan) at 229 nm to determine the amount of sotalol released to receptor compartment. The release profiles of sotalol from monolithic films were given in Fig.2 and Fig. 3. Drug release kinetics evaluated by GhraphPad Instat 3.0 computer programme are presented in Table 3.

Analytical validation of spectrophotometric analysis for quantization of sotalol in HEPES buffer was done by performing linearity and range, precision, accuracy and specificity according to ICH Guidelines Q2R1 (24). Accuracy with the existence of minor components was found as 97.6 % with RSD of 1.7 % also indicated specificity and intermediate precision was obtained ($P>0.05$). Additionally, low value for standard error of slope (0.039 ± 0.0003) and

good correlation coefficient value (r^2=0.9999) established the linearity of the method in concentration range of 1-28 µg/mL with a LOQ value of 0.115µg/ml.

Morphological Analysis

The external morphology of selected monolithic films (F4, F4C and F4D) were analyzed by scanning electron microscopy (SEM) (Jeol JSM 6490LV, Tokyo, Japan). Samples were sputtered under an argon atmosphere with gold to a thickness of 8 nm and were then observed with microscope at room temperature with a magnification of 200 and 2000, 15 kev for micrographs (10). The micrographs of SEM analysis were given in Fig. 4A, 4B and 4C.

RESULTS and DISCUSSION

Characterization of films

Each individual film formulation given in Table 1 was investigated in thickness, drug homogeneity and swelling characteristics are given in Table 2.

Table 1. Compositions of films given in mg.

Codes	Sotalol	E100	RL100	*NE40D	AA	CA	DBS
F1	20.6	-	686	-	-	-	140
F2	20.6	686	-	-	-	-	140
F3	20.6	-	343	860	-	-	140
F4	20.6	343	-	860	-	-	140
F4A	20.6	343	-	860	10.3	-	140
F4B	20.6	343	-	860		10.3	140
F4C	20.6	343	-	860	34.3	-	140
F4D	20.6	343	-	860	-	34.3	140

*NE40D is 40 % w/w dispersion of Eudragit polymer in aqueous solution

Film characterization studies were evaluated by means of thickness, drug content and swelling percentage of polymeric films. As seen in Table 2 closer values of thickness were obtained from different films. Variation among the films was attributed to difference in raw materials; especially the polymers. However, the essential point in these results was low standard deviation (SD) values, which was interpreted as the reproducibility of preparation method for each individual film formulation.

Table 2. Characterization of films.

Film code	[a] Thickness (mm) ± SD	[a] Drug content (mg/cm^2) ± SD	[b] Change in thickness % ± RSD	[b] Percentage Swelling Is % ± RSD
F1	0.353 ± 0.006	0.890 ± 0.027	28.5 ± 0.50	275.3 ± 15.1
F2	0.377 ± 0.021	0.880 ± 0.041	7.33 ± 0.29	17.21 ± 3.69
F3	0.350 ± 0.019	0.958 ± 0.014	45.8 ± 1.06	141.6 ± 5.86
F4	0.340 ± 0.012	0.802 ± 0.053	17.6 ± 4.15	28.61 ± 1.35
F4A	0.375 ± 0.025	0.895 ± 0.026	6.99 ± 0.32	16.38 ± 3.82
F4B	0.377 ± 0.021	0.821 ± 0.034	6.60 ± 1.37	34.87 ± 1.51
F4C	0.383 ± 0.032	0.884 ± 0.035	10.1 ± 2.50	19.41 ± 1.88
F4D	0.360 ± 0.026	0.862 ± 0.019	28.5 ± 0.50	26.87 ± 4.31

[a] n=9, [b] n=3, for uniformity in thickness and drug contents 3 different discs were studied from each batch and 3 batches were investigated for each formulation.

When the uniformity of drug amounts in films was evaluated, mostly high drug amounts were determined with low SD values (Table 2). Drug content was slightly higher for the films prepared with RL100 and SD values were smaller for this group. This could be attributed to the better solubility of sotalol in RL100 polymer, supported by Verma et al (6). When the effects of adipic acid (F4A, F4C) and citric acid monohydrate (F4B, F4D) on drug amount and homogeneity were compared in F4 film, it was found that pore formers slightly decreased the drug content; however they provided smaller SD values than F4 which could be interpreted as; sotalol could be better dispersed in films with the existence of adipic or citric acids. In general, the results indicated that, the preparation method was sufficient for the reproducibility of the films and it was observed that; films were more flexible prepared by using E100 polymer rather than RL100 as film compound.

Characterization of In vitro Release

Investigated polymers have zwitter ionic (RL100), cationic (E100) or non-ionic (NE40D) properties in their nature. All these polymers have different swelling properties related with type and amount of their functional groups. In our study, films containing RL100 polymer coded as F1 and F3 gave higher degrees of swelling (Table 2, Fig.1) accompanied with higher *in vitro* release amounts of drug (Fig. 2). This was attributed to increasing permeability of RL100 by taking of water to the inside of film related with its QAGs (F1 and F3) (18, 25). According to Yasuda's "free volume theory", a higher degree of swelling of membrane would result in longer free volume available for diffusion of water-soluble drug and higher permeability concomitant to higher release of drug could be obtained attendantly (25).

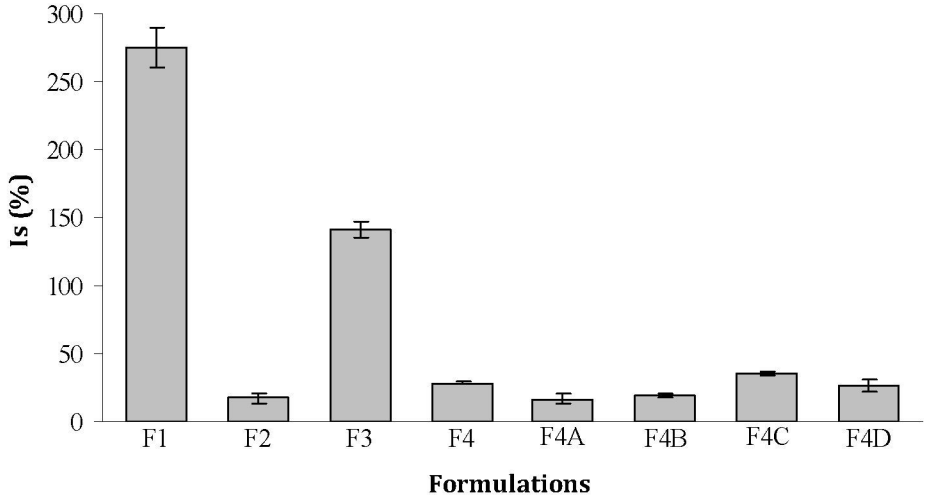

Figure 1. Swelling properties of films.

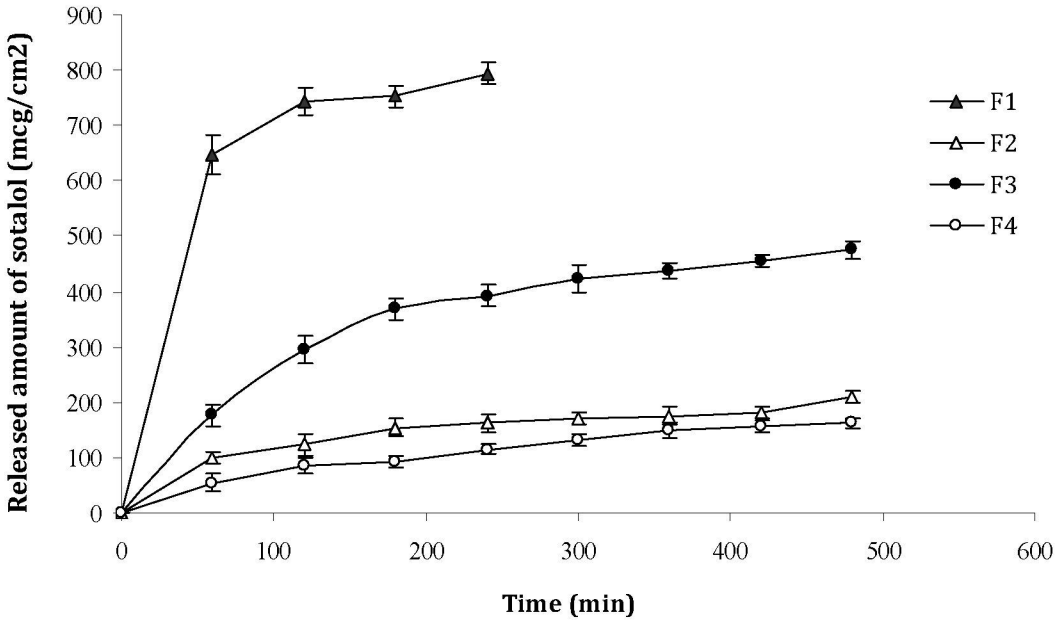

Figure 2. Drug release profiles of F1, F2, F3 and F4.

Comparison of formulations according to main polymer groups resulted as a similar trend in drug release; while the formulations containing RL100 (F1,F3) gave higher release rates, the ones containing E100 (F2,F4) gave the slower release rates due to lack of QAGs (25,26). The QAGs had effect on swelling of film and release of cationic sotalol. This effect resulted as higher swelling degrees and a burst like release characterized a high initial release followed by a slow release of drug. This could be attributed to the repulsive forces between the cationic or zwitter ionic polymers and cationic sotalol (25). It is observed that the type of polymer and drug by means of containing a functional group like QAGs have a great influence on the release of drug from that kind of films (26). Between these formulations F4 containing E100 and NE40D gave the slowest release of drug and it was selected for investigation of effects of pore formers on the release of drug. In addition, F4 formulation has an advantage of providing homogeneous dispersing of water-soluble organic acids in film due to high water content of NE40D. Two different ratios (1.5 % or 5% w/w) of adipic acid or citric acid monohydrate were added to F4 formulation to form F4A-F4C and F4B-F4D formulations respectively (Table1). The formulations containing either adipic or citric acid showed that existence of organic acids had no effect on swelling degrees of the films (F4A and F4B) (Fig. 1). However, increase in amount of acid content resulted as an increase in swelling degrees of films (F4C and F4D) (Fig. 1). In drug release, especially adipic acid caused a rapid release probably due to degradation in polymer chains of F4A and F4C (Fig. 3). This effect could be explained by the low pKa value and low aqueous solubility of adipic acid (27) which creates acid micro-chambers inside of polymer matrix that leading degradation of chains. In the existence of citric acid monohydrate, the release of drug was again increased from F4B and F4D compared to F4 formulation, unless it was not as increased as F4A and F4C films formulated with adipic acid (Fig. 3). That could be explained by higher pKa value and higher water solubility of citric acid than adipic acid, so that citric acid easily leave the film by dissolving in relatively alkaline buffer medium (27, 28).

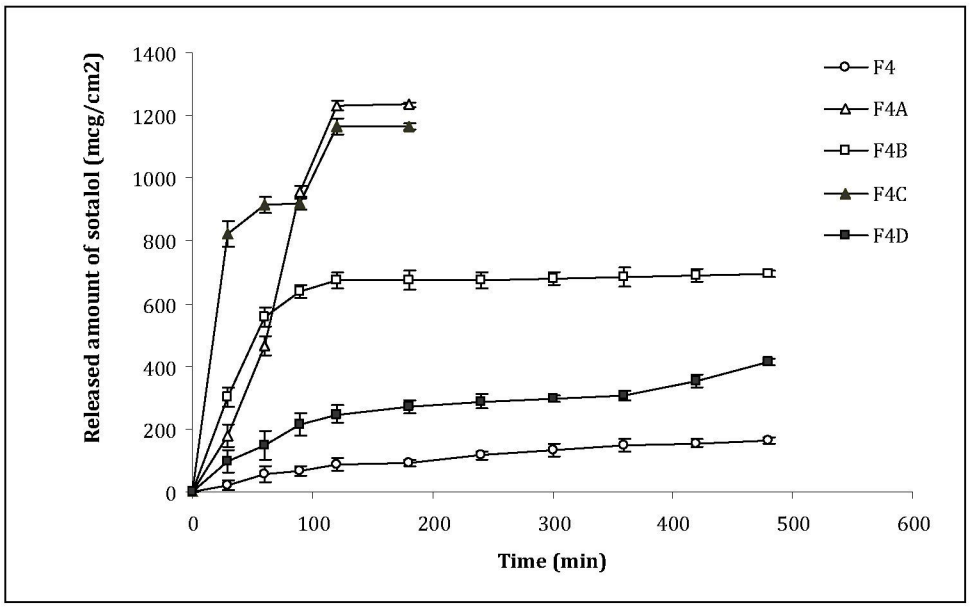

Figure 3. Release profiles of F4, F4A, F4B, F4C and F4D films.

SEM analysis presented in Fig. 4 supported the data of film characterization and release properties. In Fig. 4A, sotalol crystals could be seen in F4 film after 1 hour of release study. However, it can be seen that crystal structures were disappeared in micrographs of F4C containing adipic acid and F4D containing citric acid monohydrate presented in Fig. 4B and 4C respectively. It can be inferred that sotalol was totally discharged from the films (F4C and F4D) in 1 hour. This finding was also supported with the release rate data of sotalol from the films (Fig. 3).

Data of drug release kinetics obtained from investigated films are presented in Table 3. According to higher determination coefficient (r^2) and lower residual mean square values (RMS), most of the formulations could be accepted as best fitted to Korsmeyer-Peppas kinetic model. Korsmeyer-Peppas kinetics could not be able to calculate from release data of F4A, F4B and F4C films due to burst release of drug from these formulations. The *n* values of Korsmayer-Peppas kinetics indicated that amount of drug released by Fickian diffusion ($n<0.500$) predominated from the most of formulations as seen in Table 3 (3, 4, 29).

Table 3. Kinetic evaluation of drug release from films.

Kinetic Parameter	F1	F2	F3	F4	F4A	F4B	F4C	F4D
Higuchi								
r^2	0.9599	0.9424	0.8784	0.9460	0.9210	0.5308	0.8138	0.9239
k_H	5.2950	0.9008	1.7260	0.7412	19.550	1.924	2.6950	1.8670
RMS	21.512	1.844	11.394	0.8666	122.59	116.3	13.510	10.208
Korsmeyer-Peppas								
r^2	0.9589	0.9443	0.8915	0.9550	**	**	**	0.9346
n	0.2782	0.4320	0.3694	0.5107				0.4568
RMS	0.0244	0.0021	0.0018	0.0013				0.0026

* r^2 indicates determination coefficient; k_H is kinetic constant, n is diffusional exponent indicative of the mechanism of drug release, RMS is residual mean squares.
** burst effect

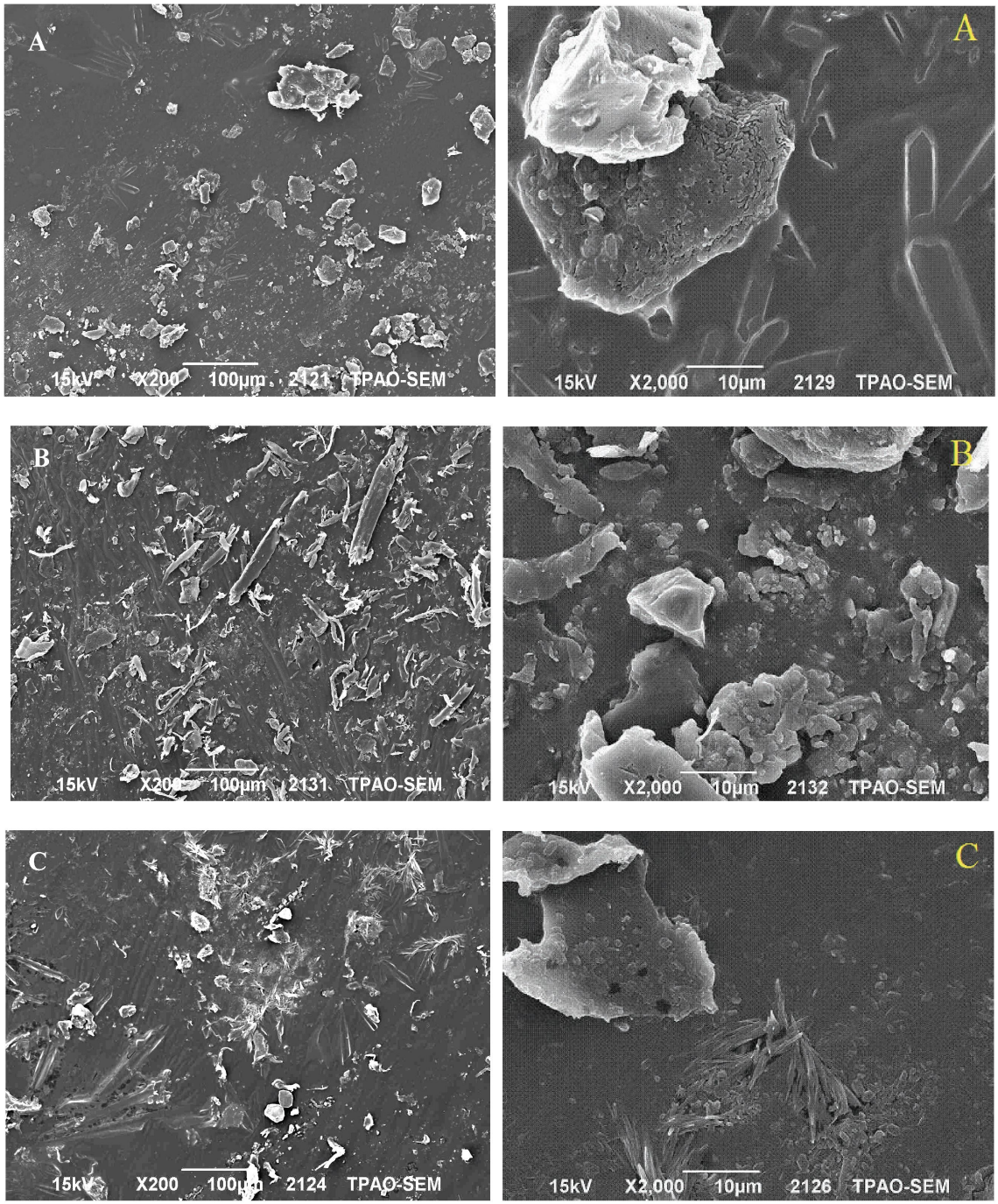

Figure 4. SEM micrograph of F4 (A), F4C (B) and F4D (C) formulations withdrawn from dissolution medium at the end of 1h release study.

CONCLUSION

As a conclusion characterization studies on monolithic films of sotalol prepared by Eudragit polymers evaluated by means of thickness and drug content uniformity indicated that the reproducibility of film preparation method was sufficient. The type of polymer used and nature of drug incorporated influenced the release of drug from films. Cationic drug rapidly released from zwitter ionic polymers followed by a slow release. High swelling capacities of polymers, which increased the permeability of films, resulted as a burst like release of drug. The existence of organic acids inside of the film increased the release of drug and acid pKa value accompanied low aqueous solubility of adipic acid caused a burst like release from cationic polymer based films.

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