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ORIGINAL ARTICLE / ÖZGÜN MAKALE

INVESTIGATING THE EFFECT OF pH AND ION STRENGTH ON LOADING AND RELEASE PROPERTIES OF DIFFERENT ION EXCHANGERS

pH VE İYON KUVVETİNİN İYON DEĞİŞTİRİCİLERİN YÜKLEME VE SALIM ÖZELLİKLERİ ÜZERİNE ETKİSİNİN İNCELENMESİ

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ABSTRACT

Objective: *Ion-exchangers are inert, water-insoluble polymers with ionizable functional groups on their surface. They can be used for purposes such as disintegrating or taste masking in orally disintegrating dosage forms, or they can provide a pH-dependent controlled release.*
Material and Method: *The loading and release properties of different cation exchangers were investigated by loading Atenolol to Amberlite CG50, Dowex 50W-X2 and Smopex 101 as weak or strong resin and strong fiber, respectively. The effect of the ionic strength of the medium on the loading capacities of these materials were investigated in water and pH 7.4 HEPES buffer using batch method and loading was monitored by pH, zeta potential, FTIR and SEM analysis. Loading capacity was calculated UV spectrophotometrically. The effect of pH and ionic strength on the atenolol release was investigated by the dialysis bag method in pH 1.2 HCl, pH 6.8 PBS and pH 6.8 HEPES media.*
Result and Discussion: *Due to its low molecular weight and high pKa atenolol was successfully loaded with a capacity over 93%. As the pH could be balanced a higher loading capacity was achieved in HEPES buffer. The decrease in zeta potential values proved that the complexes were successfully obtained and the ionic complex formation was also monitored with FTIR and SEM micrographs. Atenolol did not get released in pH 1.2 medium, contrarily to pH 6.8 in which the functional groups are ionized. The higher amount of counter ions in PBS buffer also affected the release. The highest release rate was obtained with Amberlite. All ion-exchangers provided a pH-dependent release fitting to Higuchi or Zero order kinetics that shows diffusion. Boyd equation results also showed that diffusion mechanism was particle controlled.*
Keywords: *Amberlite CG50, atenolol, cation-exchange materials, Dowex 50W, Smopex 101*

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ÖZ

Amaç: *İyon değiştiriciler, yüzeylerinde iyonize olabilen fonksiyonel gruplar bulunan suda çözünmeyen inert polimerlerdir. Ağızda dağılan dozaj formlarında dağıtıcı veya tat maskeleyici gibi amaçlar için kullanılabilirler veya pH'ya bağlı kontrollü salım sağlayabilirler.*

Gereç ve Yöntem: *Atenolol kullanılarak üç farklı katyon değiştiricinin yükleme ve salım özellikleri araştırılmıştır. Kullanılan katyon değiştiriciler zayıf veya kuvvetli reçine ve kuvvetli fiber olarak sırasıyla Amberlite CG50, Dowex 50W-X2 ve Smopex 101 olarak seçilmiştir. Ortamın iyonik kuvvetinin bu malzemelerin yükleme kapasitelerine etkisi, beç yöntemi kullanılarak su ve pH 7.4 HEPES tamponunda araştırılmış ve yükleme pH, zeta potansiyeli, FTIR ve SEM analizi ile izlenmiştir. Yükleme kapasitesi UV spektrofotometrik yöntemle hesaplanmıştır. Ortam pH değeri ve iyonik kuvvetinin salım üzerindeki etkisi diyaliz torba kullanılarak pH 1.2 HCl, pH 6.8 PBS ve pH 6.8 HEPES ortamlarında incelenmiştir.*

Sonuç ve Tartışma: *Atenolol düşük molekül ağırlığı ve yüksek pKa değeri nedeniyle % 93'ün üzerinde bir kapasite ile başarıyla yüklenmiştir. pH dengelenebildiğinden, HEPES tamponunda daha yüksek bir yükleme kapasitesi elde edilmiştir. Zeta potansiyel değerlerindeki düşüş, iyon değiştirici-etken madde komplekslerinin başarılı bir şekilde elde edildiğini kanıtlamıştır. İyonik kompleks oluşumu FTIR ve SEM mikrografları ile de görüntülenmiştir. Atenolol, fonksiyonel grupların iyonize olduğu pH 6.8'in aksine pH 1.2 ortamında salınmamıştır. İçerdiği karşıt iyonlar nedeniyle PBS tamponunda daha yüksek miktarda salım sağlanmıştır. En hızlı salım Amberlite ile elde edilmiştir. Tüm iyon değiştiriciler, difüzyonu gösteren Higuchi veya Sıfır derece kinetikle pH'a bağlı bir salım göstermiştir. Boyd eşitlik sonucuna göre salım aynı zamanda partikülden kontrolle gerçekleşmiştir.*

Anahtar Kelimeler: *Amberlite CG50, atenolol, Dowex 50W, katyon değiştiriciler, Smopex 101*

INTRODUCTION

Ion exchange mechanism has been used in several scientific areas related to pharmacy from the beginning of the 20th century; such as in water purification since 1930s, and in pharmaceutical and biomedical applications since 1950s [1-4]. Nowadays, ion exchangers are frequently used in fast disintegrating oral dosage forms as superdisintegrants or taste masking agents, especially in pediatric dosage forms [5-7]. Ion exchanger-drug complexes can also be effective in increasing storage stability of drugs. They can be used as pH-dependent carrier systems for ionic drugs and can be prepared in the form of oral dosage forms like films, tablets, capsules, or suspensions with sustained release properties [2, 8-10]. Moreover, ion-exchange resins and fibers are also under investigation since early 1990s as drug carrier systems in transdermal delivery alone or with the combination of iontophoresis and as wound dressing [11-14].

Classification of Ion Exchangers

The ion exchange resins and fibers consists a static polymer structure with functional groups on their surfaces. These groups can either be in acidic or basic form that can interchange their ions with the counter-ions of the medium. Due to the charge of the functional groups resins and fibers can be classified as cation or anion exchangers. The type of functional groups also affects the material properties being as strong or weak ion exchangers [1,4,15]. The main difference between resins and fibers comes from the cross-linkage of polymer skeleton; generally, the resins consist cross-linked polymer structure while the fibers do not [16-17].

Strong cation exchange resins generally consist of cross-linked polystyrene-divinyl benzene polymer structure with sulfonic acid (-SO_3H) groups, which have been prepared by the polymerization of polymer with sulfuric acid or chlorosulfonic acid. Dowex 50, Amberlite IR 120, and Amberlite IRP69 are some of the commercial examples of these resins. Weak cation exchange resins with carboxylic acid (-COOH) functional groups are prepared by polymerization of organic acids, such as acrylic or methacrylic acid in the presence of a cross-linking agent such as divinyl benzene to yield cross-linked networking. Some commercial examples are Amberlite IRC 50, Amberlite IRP64 and IRP88 [2,4].

In the case of anion exchange resins, cross-linked polystyrene polymers produced by chloromethylation of polystyrene beads with subsequent treatment with ammonia, primary, secondary,

or tertiary amines are used in production. Dowex 1, and Amberlite IR 400 are examples of strong anion exchange resins having quaternary ammonium groups, while Dowex 2 and Amberlite IR 4B are weak anion exchangers, which have predominantly tertiary amine substitutes [2,4].

The resins can also be classified due to their structure as gel-type (microporous) or macroporous type. Gel-type resins have lower cross-linked structure and a smoother surface while macroporous ones have a sponge-like structure with higher cross-linking [18].

Despite the resins, fibers consist of non-crosslinked hydrophobic polymer chains such as polypropylene or polyethylene as skeleton that carry a constant positive or negative electrical charge located on the surface of the fiber. Due to these negative or positive electric charges, they are called as cationic or anionic exchangers, respectively. Because of their larger surface area compared to resins, fibers provide a higher loading capacity. Besides they have good mechanical and thermal strength and chemically inert structure [16,17]. Smopex types (Smoptech Ltd., Turku, Finland) are one of the commercial examples of ion exchange fibers. Among them, a cation exchange type of Smopex 101 is composed of styrene sulfonic acid grafted polypropylene, whereas Smopex 102 is an acrylic acid grafted polypropylene fiber. Some other anion-exchange examples of Smopex are 103pe and 105pe types with uncrosslinked cellulose grafted polyethylene side chain skeleton and vinylpyridine ion exchange groups [16,19-20].

Ion Exchange Mechanism

The ion exchange mechanism of resins depends on the reversible interchange of the surface bounded ions with the ions of the same charge in the medium. This process also involves the competition of the counter-ions of the medium [1]. The ionic strength and pH of the medium, and the ionization, pKa, molecular weight properties of the drugs plays important role for both loading and release from the resins [4]. Unlike the resins, the ion exchange in fibers is occurred on a non-crosslinked and non-porous surface that affects the ionic reaction. The ion-exchange in resins and fibers are generally explained by Donnan principle and diffusion process [16,17].

In this study, the loading and release properties of different cation exchangers were compared by loading Atenolol (ATN) to Amberlite CG50, Dowex 50W-X2 and Smopex 101. Among the ion exchangers, Amberlite CG50 is a weak cation exchange resin with carboxcylic acid (–COOH) functional group containing macroporous methacrylate structure. Contrarily, strong cation exchange resin Dowex 50W-X2 contains sulfonic acid (-SO_3H) functional groups on gel type (microporous) divinyl benzene structure. Strong cation exchange fiber Smopex 101 also contains -SO_3H functional groups in non-crosslinked and non-porous polypropylene structure. The effect of pH and ionic strength of the medium on loading and release to these ion exchangers were investigated using water or pH 7.4 HEPES buffer as loading media and pH 1.2 HCl, pH 6.8 PBS or pH 6.8 HEPES as release media. ATN, which is a well-known β-blocker drug used for cardiovascular diseases, such as hypertension, angina pectoris, arrhythmias, and myocardial infarction was chosen due to its pKa of 9.5, good solubility and the cyclic structure of the molecule that causes a bitter taste [21].

MATERIAL AND METHOD

Materials

Atenolol (Abdi İbrahim; ATN), Dowex 50W-X2 (Dow Corning; DW), Amberlite CG50 H^+ type (Acros Chem; AMB), Smopex 101 (AlfaAesar; SMP), 4-(2-hydroxyethyl)-1-piperazineethanesulphonic acid (HEPES; Fluka), K_2HPO4 (Merck), NaOH (Merck), HCl (Merck), Dialysis tube MWCO 14000 (Sigma) were used. Water was used as 18.2 mΩ quality purified (Millipore) in all experiments.

Spectrophotometric Analysis of ATN

The UV spectrophotometric calibration of ATN was done in different media for drug loading and release studies. Briefly, water and pH 7.4 HEPES buffer media were used for loading studies and pH 1.2 HCl, pH 6.8 PBS, pH 6.8 HEPES media were used for release studies. The UV spectrophotometric calibration of ATN were separately done in all media studied. The calibration study parameters were as follows:

UV calibration of ATN in 18.2 mΩ water and pH 1.2 HCl media were done with the concentrations of 2.5, 5, 10, 12, 14, 16, 20 and 24 µg/ml obtained by diluting the 100 mg/ml stock solution. The calibration of ATN in pH 6.8 PBS, pH 6.8 and pH 7.4 HEPES media were done with the concentrations of 5, 10, 20, 30, 40, 60, 80, 100, 120, 140 160 µg/ml obtained by diluting the 500 µg/ml stock solution. The absorbance values of the solutions at these concentrations were read with a UV spectrophotometer (UVmini 1240, UV-Vis Spectrophotometer, Shimadzu) at 274 nm for all the buffers studied. The absorbance versus the concentrations were graphed and the calibration equations were obtained with the calibration line.

Production of Drug-ion Exchanger Complexes

Ion exchanger-drug complexes of ATN were prepared by batch method [22]. Briefly, the cation exchange resin (Dowex or Amberlite) and fiber (Smopex) particles were purified with absolute alcohol and 18.2 mΩ quality water (Merck Millipore) and dried before use. Cation exchangers were separately weighed in equal amount with ATN (1:1 ratio; 50 mg) and were mixed with the drug in 100 ml medium at 500 rpm using magnetic stirrer. The loading media were water and pH 7.4 HEPES buffer, respectively. The resulting complexes were washed with 18.2 mΩ water, filtered from 0.45 µm filter paper under vacuum and dried in an oven at 40°C overnight. The composition of the complexes and the media used in production are given in Table 1.

Table 1. Composition of drug-ion exchanger complexes and the media used in production

Ingredients/Code	F1	F2	F3	F4	F5	F6
Atenolol (mg)	50	50	50	50	50	50
Amberlite CG50 (mg)	50	-	-	50	-	-
Dowex 50-X2 (mg)	-	50	-	-	50	-
Smopex 101(mg)	-	-	50	-	-	50
Water (ml)	100	100	100	-	-	-
pH 7.4 HEPES Buffer (ml)	-	-	-	100	100	100

***In vitro* Characterization of Drug-ion Exchanger Complexes**

Drug loading capacity

Drug loading capacity was calculated from free drug remained in the medium (n=3). Briefly, 500 µl sample was taken from the 100 ml medium in 5, 15, 30, 45, 60, and 90th minutes and same amount of fresh buffer was added. Samples were centrifuged at 10.000 rpm for 2 min (Hettich ultrasantrifuge) and the aliquots were read spectrophotometrically at 274 nm. Percentage of drug loading was calculated from the amount remained in the medium with the following equation:

Loading capacity (%) = (C_0-C_t/C_0) x100

C_0 : Initial drug amount in the medium (mg)

C_t : Drug amount remained in the medium at predetermined time intervals (mg)

pH

The pH of the loading medium was investigated at certain time intervals using a pH-meter.

Zeta potential

In order to evaluate the zeta potential value of ion exchangers and the resultant complexes the dried particles were dispersed in 18.2mΩ water and immediately measured with Zetasizer (Nano-ZS, Malvern Instruments). All studies were conducted in triple.

Particle Size and Distribution

Laser diffraction (Mastersizer 3000; Malvern) analysis was carried out with a 1:10 (v/v) dilution of the ion exchange resins in water at 25°C. The detector was fixed at an angle of 90°. Data on particle size was characterized by Dv50 value that refers to the volume distribution at which 50% of the sample is smaller or larger. The size distribution was calculated by the equation of ´Span=(D90–D10)/D50´.

Fourier Transform Infrared (FTIR) Studies

The ion exchange mechanism was monitored on ion exchanger-drug complexes by scanning the existence or loss of the characteristic stretching bands of materials using Cary 630 FTIR (Agilent Technologies).

Scanning Electron Microscopy (SEM) Analysis

Surface morphology of the ion exchanger-drug complexes were examined using a scanning electron microscope (Quanto 200F, Fei) equipped with a digital camera at 5 kV accelerating voltage. Samples were sputter-coated with gold-palladium before use.

In Vitro Dissolution Studies

In vitro ATN release from ion exchanger-drug complex was studied by dialysis bag method in pH 1.2 and pH 6.8 media. Briefly, dialysis bags with MWCO 12000-14000 were saturated with appropriate buffer for overnight and then filled with the ion exchanger-drug complex equivalent to 10 mg of ATN. The dissolution studies were conducted for 2 hour in pH 1.2 HCl and then 6 hours in pH 6.8 PBS or pH 6.8 HEPES media. A thermostatic incubator was used at 37°C and 100 rpm (MaxQ 4450, Thermoscientific). 1 ml of sample was taken at 15, 30, 60, 90 and 120th min for pH 1.2 and 15, 30, 60, 120, 180, 240 and 360th min for pH 6.8, respectively. The analysis was done spectrophotometrically at 274 nm.

As the ion exchange mechanism can be explained by diffusion process, ATN release was evaluated using Korsmeyer-Peppas, Higuchi and Zero order kinetics. The Higuchi model was used to explain the Fickian diffusion using the drug release versus square root of time plot, while the n value in the Korsmeyer-Peppas $Mt/M\infty=Kt^n$ equation was used to investigate the type of release mechanism. The n values between 0.45 and 0.85 indicates the non-Fickian diffusion for swelling controlled transport whereas the values above 0.85 indicate zero order kinetics (case II transport mechanism) [7,8].

Boyd kinetics was also performed for evaluating the rate-limiting step. Here, for the released fraction (F) under 85 % the below equation is used:

$$F = Mt/M\infty = 1 - 6/\pi^2 \sum e^{-n^2Bt}/n^2$$

where B represented the rate constant, Mt and M∞ are the amounts of drug released after time and after infinite time. This equation can be simplified for the F values lower than 0.85 as;

$$Bt = 6.283 - 3.290F - 6.283(1 - 1.047\ F)^{1/2}$$

If the released fraction against time (Bt plot) is found linear in the equation, the rate limiting step for drug diffusion can be assumed as the resin matrix [22].

RESULT AND DISCUSSION

ATN Loading onto Different Cation Exchangers

The drug-ion exchanger complexes were produced by the batch method. In this method the ion exchanger is simply mixed in a known concentration and volume of drug solution in a beaker to provide an ion exchange between the drug and surface functional groups of the resin or fiber. The effective parameters on ion exchange mechanism and therefore drug loading are related with the properties of drug and resin/fiber and the loading conditions. The structure, miliequivalent (mEq) exchange capacity and cross-linking property of the resin or fiber; the molecular weight, existence of aromatic ring and

pKa of the drug; mixing rate or time, drug:ion exchanger ratio, pH and ionic strength of the media affect the drug loading with the batch method [2,4].

In this study, ATN was successfully loaded onto the ion exchangers in 1:1 ratio in both media and the optimum time for loading was chosen as 30 minutes as the pH value did not show dramatic change afterwards. Loading capacities in HEPES buffer were slightly higher than in water due to the existence of counter ions inside the buffer (Table 2).

Table 2. pH change during loading process and loading capacities obtained in different media, n=3

	pH values					
Medium	**Water**			**HEPES**		
Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0	9.68 ± 0.01	9.60 ± 0.02	9.65 ± 0.02	7.58 ± 0.02	7.56 ± 0.01	7.59 ± 0.01
5	8.20 ± 0.10	8.80 ± 0.08	9.11 ± 0.15	7.45 ± 0.06	7.43 ± 0.05	7.53 ± 0.04
15	6.96 ± 0.04	6.00 ± 0.01	8.90 ± 0.02	7.43 ± 0.06	7.42 ± 0.02	7.52 ± 0.03
30*	8.00 ± 0.06	6.77 ± 0.03	8.91 ± 0.03	7.46 ± 0.04	7.42 ± 0.02	7.54 ± 0.03
45	8.00 ± 0.03	6.70 ± 0.02	8.91 ± 0.05	-	-	-
60	-	-	-	7.46 ± 0.02	7.45 ± 0.03	7.46 ± 0.04
90	-	-	-	7.44 ± 0.04	7.42 ± 0.02	7.44 ± 0.07
*Loading capacity (%)	93.51 ± 0.350	98.37 ± 0.300	93.14 ± 0.350	99.90 ± 0.003	99.87 ± 0.027	99.90 ± 0.005

*****30 min was chosen as optimum loading time

One of the parameters that affects loading is the ionization characteristics of the ion exchangers. Among the chosen materials, Dowex resin with pKa value of 1-2, is strongly acidic, therefore the ion exchange and the drug loading or drug release was affected from the ionic strength of the medium rather than the pH change [23]. Contrarily, Amberlite shows weak acidic properties with pKa 4-6 and the ion exchange mechanism was affected from the pH of the medium. As both of the resins were in ionized state during loading process, ATN could be successfully loaded in water and HEPES media. Smopex fiber has been totaly ionized at pH 7.4 due to its lower pKa (pKa 0-1) [19]. Therefore, ATN could also be loaded onto fiber in both media. Loading ratio of ATN was slightly higher in pH controlled environment (Table 2).

Another property affecting ATN loading is the ion exchange capacity of the resins/fibers. Generally weak acidic resins have higher capacities than strong ones. In this study the weak acidic resin Amberlite CG50 was a bidendate –COOH resin with 10 mEq/g capacity, whereas Dowex 50W was a strong resin with $–SO_3H$ and 4-6 mEq/g capacity. Also strong acidic fiber Smopex 101 had $–SO_3H$ and 4.1 mEq/g capacity. All ion exchangers were regenerated before use for providing a total loading capacity, as they were in H^+ form commercially. However, ATN loading did not get affected from the total ion exchange capacity as the drug molecule did not have high molecular weight. Besides, the high pKa and aromatic structure of ATN had advantages on loading. It is reported that the aromatic ring existence of drugs highly affects the ion exchanger-drug interaction as the counter-ions of aromatic rings show higher affinity to the ionized functional groups of resins and fibers [17].

pH Values

Measurement of pH change is a way to monitor the complex formation, especially when the column process is used in production [22]. Returning to initial pH value or a balanced pH can be considered as the ionic complexation.

In this study, initial pH value of ATN stock solution in water was measured as pH 9.6. Addition of acidic resins decreased this pH value down to 6.0 in the presence of Dowex; pH 6.96 in the presence of Amberlite despite to Smopex fiber, in which significant pH change was not observed (Table 2). Contrarily, ATN solution in HEPES buffer provided a controlled pH value between 7.56-7.59 initially, which slightly dropped with the addition of ion exchanger and remained more balanced than water medium throughout the experiment. Therefore, ATN was able to be loaded by 99.9% under conditions with constant pH and the addition of counter-ions that do not compete with the drug. However, maximum loading was determined as 93% for Amberlite and Smopex in the water medium. Reasonably,

this could be due to the absence of counter-ions in water medium that causes ATN to be released back for maintaining the ionic balance.

Zeta Potential Values

Controlling the zeta potential value can be a diagnostic tool in the prediction of complexation between the ion exchanger and the drug. A significant change in zeta potential value can be interpreted as the existence of ionic complexation.

The ionized functional groups of the cation exchangers provide a negatively charged zeta potential in alkaline solutions because of the hydroxyl ion attack to the surface. In case of strong cation exchangers, a negatively higher zeta potential value can be expected due to the protonozation of strong acidic functional groups such as $-SO_3H$. Besides, the cross-linkage can also be effective on the zeta potential value of ion exchangers. It is reported that, due to the swelling the increased adsorption of water can cause lower zeta potential value in low cross-linked resins [24].

As it can be seen from Table 3, zeta values of unloaded resins measured in deionized water were found negatively charged which means that the functional groups existing on the resin surface are ionized in water. Drug free Dowex resin gave a relatively higher zeta potential value due to its sulfonic acid groups. After complexation the negative zeta values decreased significantly. In case of strong acidic fiber Smopex, the zeta potential value could not be measured reproducibly due to its rod shape with theoretically 250 µm length.

Table 3. Particle size and zeta potential characteristics of ion exchangers and drug complexes, n=3

Ion exchanger	Drug free			Drug loaded [a]		
	Dv50(µm)	**Span**	**Zeta (mV)**	**Dv50 (µm)**	**Span**	**Zeta (mV)**
Amberlite CG50 4 % cross-linkage, 75-150 µm dry size	171 ± 0.45	0.700	-23.7 ± 2.81	196 ± 2.17	0.647	-15.1 ± 2.75
Dowex 50W-X2 2% cross-linkage, 50-75 µm dry size	130 ± 1.14	0.749	-31.0 ± 5.01	138 ± 1.58	0.976	-14.9 ± 4.87

[a] F4-F6 complexes were used.

Particle Size and Distribution

The particle size and cross-linking properties are effective on the ion exchange mechanism and therefore drug loading and release. In case of resins, the decrease in cross-linking capacity causes an increase in the swelling of the particle [2,4]. Therefore, the swelling of the resins were investigated via measuring the wetted particle size of the resins using laser diffraction method with Mastersizer (Model 3000; Malvern). The results (Table 3) showed that the highest swelling was seen with Dowex resin, which also provided highest drug loading (98.37 %) in water media. This resin has a lower cross-linking capacity (2%) than Amberlite (4 %). Besides, dry resin particles of Dowex were smaller (50-75 µm) than Amberlite resin (75-150 µm) in size. Smopex, being rod shaped with high surface area and noncross-linked, non-porous structure, is reported to show less swelling than the resins [25]. However, the size of this ion exchanger was not measurable with light scattering method due to its rod shape. Its non-porous structure and high surface area was later observed with SEM studies.

It is reported that sulfonic acid functional groups are the other reason of high swelling in strong cationic resins due to the increased hydration caused by the sulfonic acid group. Therefore a higher wet size and swelling occurs. This high swelling due to the increased amount of sulfonic acid group not only affects the loading but also causes a sustained/prolonged release [26].

Ion Exchanger-drug Complex Characterization by FTIR

FTIR is a useful tool for proving the ionic complexation. If the complexation occurs the characteristic peaks related with the functional groups of both ion exchanger and the drug can either

shift or dissappear due to bonding. Therefore, the drug free and drug loaded particles investigated with FTIR.

As it can be seen from FTIR spectra (Figure 1), ATN was successfully complexed with the ionic exchangers. ATN shows an -NH stretching band due to its -NH_2 functional group, which were found at 3347 and 3158 cm^{-1} in our study (Figure 1a). Among the resins, Dowex with a divinyl benzene structure and -SO_3H functional group, generally gives characteristic strong stretching band near 3390 cm^{-1}. This band was found at 3334 cm^{-1} in our study and was disappeared in ATN-DW after ionic complexation occurred (Figure 1b and 1c). The bands at 2985-2931cm^{-1} are O-H stretching and 1686 cm^{-1} C=O stretching bands of –COOH for Amberlite (Figure 1d). The characteristic 1686 cm^{-1} C=O stretching band shifted to 1669 cm^{-1} by decreasing for Amberlite (Figure 1e). Similarly, the characteristic band related with the sulfonic acid functional group of Smopex 101 near 3436 cm^{-1} was also shifted to 3447 cm^{-1} after complexation (Figure 1f and 1g). The absence of any characteristic bands for ATN in the ion exchange complexes also revealed the ionic interaction [12].

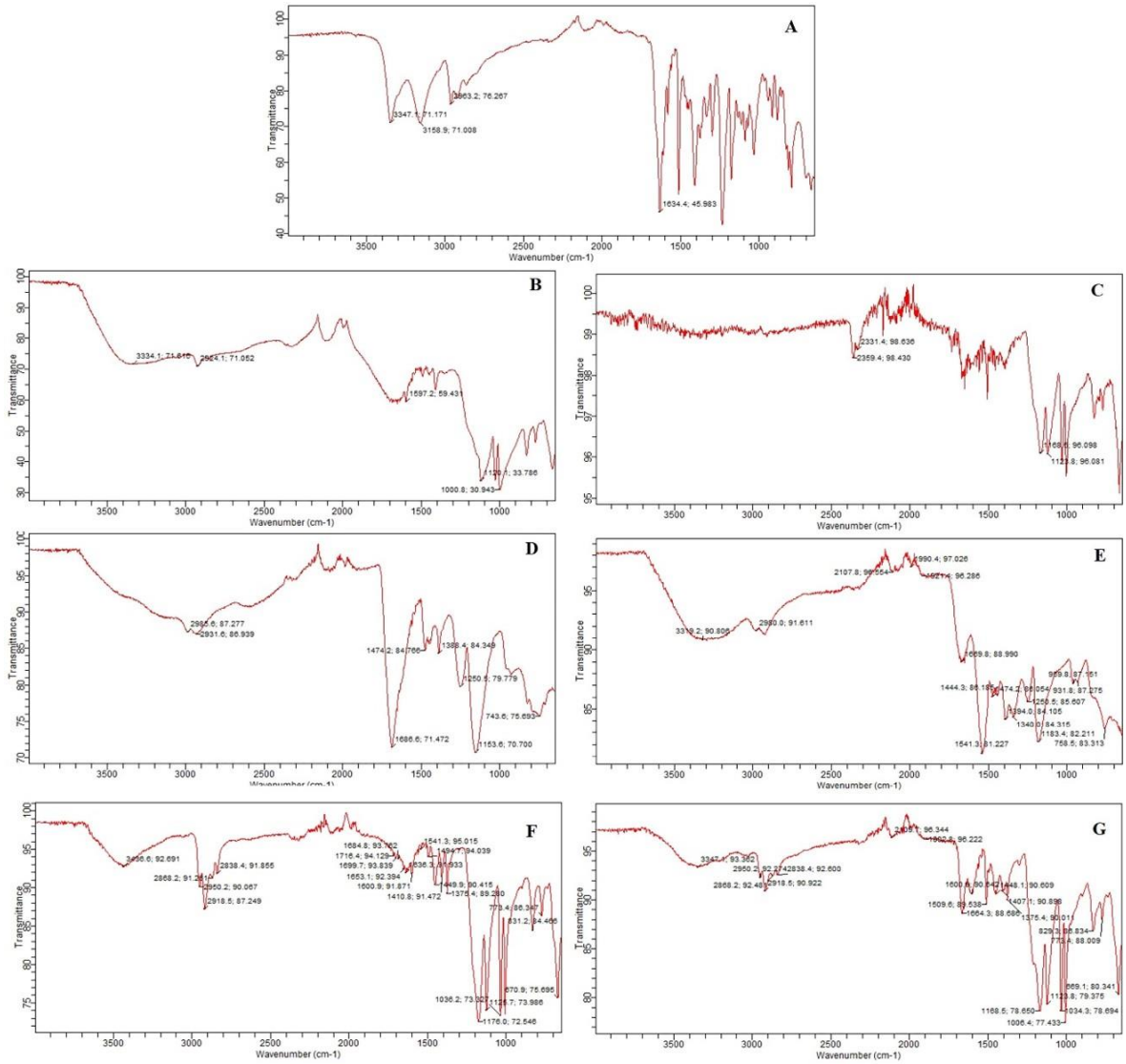

Figure 1. FTIR spectrums of; a) Atenolol, b) DOWEX resin, c) ATN-DW complex, d) AMBERLITE resin, e) ATN-AMB complex, f) SMOPEX fiber, g) ATN-SMP complex

Morphological Characterization of by SEM

Drug loaded and drug free ion exchangers were scanned using SEM. Among the chosen ion exchangers, Amberlite has a macroporous methacrylic type matrix with relatively higher crosslinked (X4) structure and bidentate –COOH groups inside the matrix. The macroporous structure of Amberlite can be seen in Figures 2A to 2C.

Sulfonated divinyl benzene resin Dowex have a spherical shape with smooth surface (Figure 2D). Since the crosslinking of this resin is low (X2) it shows more tendency to swell and take water inside. Therefore some fractures could occur on the hollow parts of the resin surfaces (Figure 2E). It is reported that these fractures has no effect on the ion-exchange mechanism [22,26]. Figure 2F shows the surface of ATN-DW complex. ATN provided an amorphous film surrounding the surface and the absence of drug crystals can be interpreted together with FTIR peaks as the ionic interaction occurred.

As it can be seen in SEM micrographs, Smopex fiber has a rod shaped non-porous structure with high surface area (Figure 2G). Its size is reported as 250 µm in length and 12 µm in diameter. Due to its non-crosslinking property, the water intake and therefore swelling is less than the resins and the drug can only be in contact with the surface of the fiber [12,17,24]. As shown in Figures 2H and 2I, ATN was loaded on the surface of this fiber and was in amorphous state.

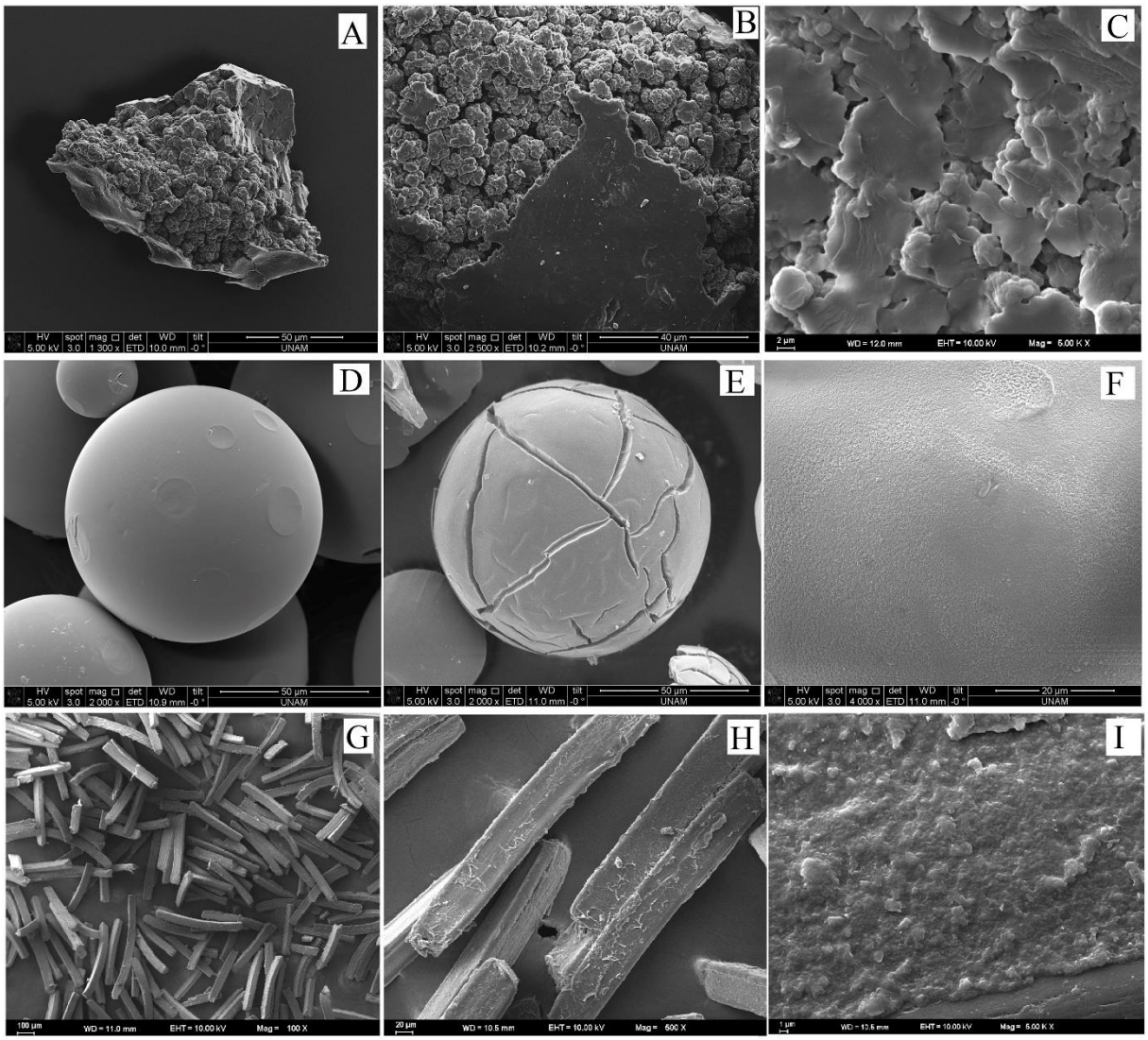

Figure 2. SEM micrographs of A) AMB, B-C) ATN-AMB (F4), D) DW, E-F) ATN-DW (F5), G) SMP, H-I) ATM-SMP (F6)

In Vitro Dissolution Studies

In vitro ATN release from ion exchanger-drug complexes was studied by dialysis bag method in pH 1.2 HCl for 2 h and pH 6.8 PBS or HEPES media for 6 h, respectively. According to the results given in Figure 3, ATN was released at pH 6.8 media while there was only neglected amount of drug release (< 1%) at pH 1.2 HCl. Even the ionization of functional groups in strong cation exchangers began from pKa 1-2, the seconder amine group of atenolol is not in ionized form in acidic pH values.

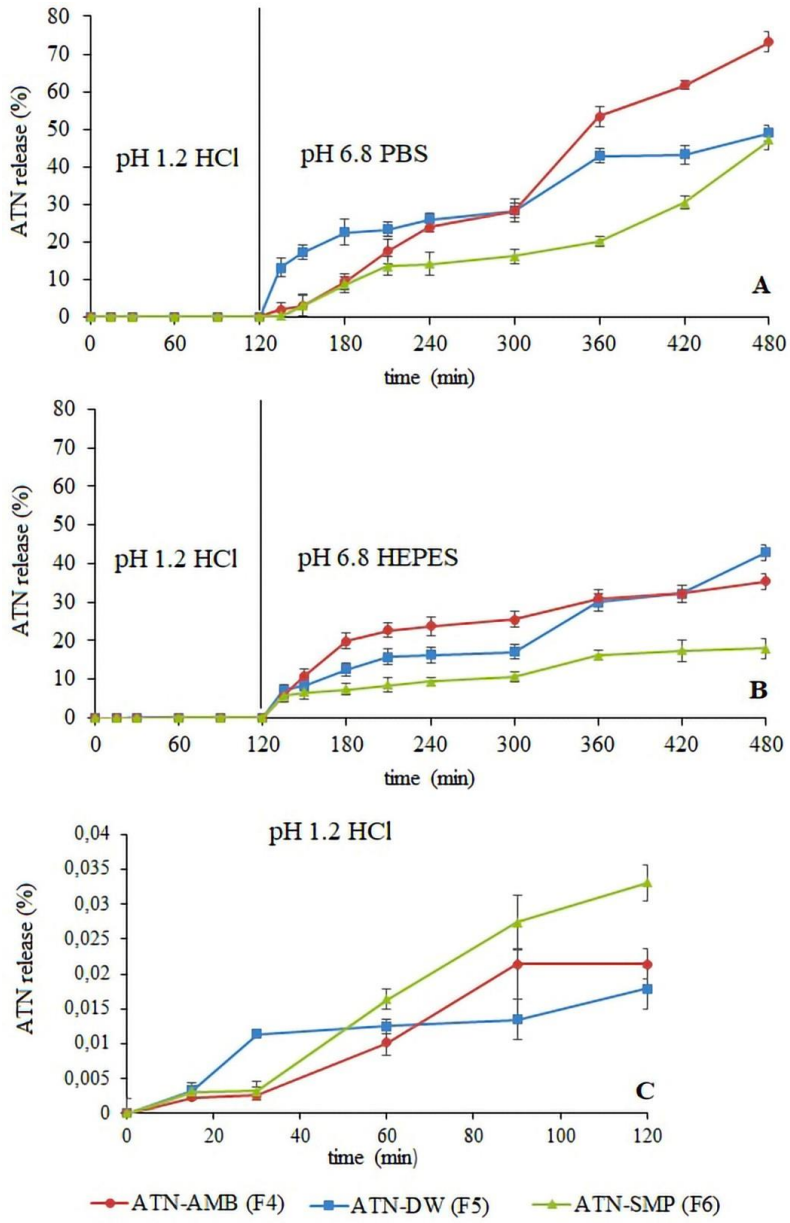

Figure 3. Atenolol release from ATN-AMB (F4), ATN-DW (F5) and ATN-SMP (F6) complexes in, a) HCl and PBS, b) HCl and HEPES and c) HCl media

ATN released at pH 6.8 media in different rates due to the ionic properties of the buffers, structure of ion exchangers used and ionization for both resins/fiber and drug. Among the buffers studied as release media, HEPES is a well-known buffer material consisting sulfonic acid, which provides a weak ionic strength that do not compete with drug ions inside. However, PBS consisting monovalent ions

such as K, Na and Cl more readily compete with the ionized ATN and is preferably bound onto the ion exchangers. Therefore the released amounts of ATN in PBS buffer were found to be relatively higher than in HEPES buffer for all type of ion exchangers.

When the release profiles were evaluated from the point of ion exchanger properties, the slowest release was achieved with the strong type Smopex fiber in both media. Being strong exchanger type, Dowex resin also provided slower release than Amberlite resin. Drug release from strong cationic resins with sulfonic acid groups are reported to be more dependent to ionic strength of the medium than the pH. The amount of sulfonic acid groups in strong cationic resins is also effective in providing a sustained or prolonged release from the complexes. The increasing amount of sulfonic acid groups results with a high swelling capacity and larger wet size, which also causes to lengthen the diffusional path [25].

In case of Amberlite resin with weak acidic macroporous structure, not only the higher capacity of ionic substituents but also the higher cross-linking percentage and particle size than the Dowex resin affected the ion exchange (Table 3). All these properties are effective not only on the loading capacity but also on the release rate. Generally a faster drug release can be expected from the resins with larger particles and higher cross-linking. Here, the degree of cross-linking is the parameter that controls the porosity of the resin structure and therefore the internal diffusion is reported to be influenced from the macroporous structure of the resin [2,27].

Release Kinetics

The effect of counter ions and ion strength on the release kinetics of drug-ion exchanger complexes were investigated by calculating zero order, Higuchi, Korsmayer-Peppas and Boyd kinetics in pH 6.8 media. Results are given in Table 4.

Table 4. Release kinetics results for pH 6.8 release media

		F4 (ATN-AMB)		F5 (ATN-DW)		F6 (ATN-SMP)	
Medium		**HEPES**	**PBS**	**HEPES**	**PBS**	**HEPES**	**PBS**
Zero order	r^2	0.8217	0.9860	0.9522	0.9020	0.9109	0.9304
	k	0.0846	0.2102	0.1011	0.1139	0.0436	0.1120
	F	36.872	564.01	159.53	73.663	81.745	106.94
Higuchi equation	r^2	0.9597	0.8940	0.9167	0.9643	0.9559	0.8418
	k	1.8720	4.0960	2.0310	2.4100	0.9147	2.1800
	F	190.52	67.444	88.530	215.83	173.59	42.564
Korsmeyer-Peppas	r^2	0.9257	0.9856	0.9283	0.9481	0.9065	0.8961
	n	0.5214	1.1870	0.5390	0.3992	0.3822	1.2980
	log k	1.7560	3.1460	1.8480	1.3710	1.7610	3.6260
	F	87.218	479.09	90.630	127.87	67.873	60.381
Boyd kinetics	r^2	0.9709	0.8618	0.8579	0.9469	0.9518	0.6937
	k	0.0004	0.0021	0.0005	0.0008	8.9×10^{-5}	0.0005
	F	266.66	49.901	48.314	142.67	157.81	18.120

Drug release from resin or fiber particles are generally explained by Donnan principle which depends on the diffusion of ions between the medium and the resin or fiber particle. This ion exchange in turn occurs by diffusion from the particle and the thin film surrounding the particle; which means that drug release is controlled from either the resin/fiber matrix or the ionic film layer surrounded by the particle, respectively. The slower release is generally considered to be the rate-limiting step in Boyd kinetics, which explains this phenomenon. Since drug release from resins and fibers occurs by diffusion, Korsmeyer-Peppas and Higuchi kinetics are also useful in explaining the drug release mechanism. Accordingly, the release can occur by non-fickian or fickian diffusion. Generally, the first case describes diffusion through a swelling matrix, while the second provides a matrix-controlled mechanism [8,22,28].

As ion exchange resins are structured from a polymer matrix, it is obvious to expect a matrix-controlled release. Therefore, Higuchi equation, which describes the release of drugs as a square root of time-based on fickian diffusion, was also applied to the pH 6.8 release data. Generally, release

mechanism from ion exchange resin complexes highly fitted to Higuchi kinetics in HEPES medium in which a slower release was achieved (Figure 3, Table 4). The results obtained in HEPES medium also fitted to Boyd kinetics that proves the particle controlled release mechanism.

The release of the drug from complexes was also fitted to Korsmeyer-Peppas equation which evaluates the fraction of drug released at time t. According to n data obtained from Korsmeyer-Peppas equation, the drug release from the ion exchangers were fitted to either fickian or non-fickian diffusion. The latter profiles also fitted to zero order release kinetics.

As a conclusion, drug loading and release was affected from the pKa of both ion exchanger and ATN, pH of the medium and the structure of the resins and fiber. Due to the existence of aromatic ring in ATN structure, the counter-ions of aromatic ring showed higher affinity to the ionized functional groups of resins. Therefore, all the ion exchangers show high affinity to ATN especially in HEPES medium. Even this affinity caused a high loading capacity in HEPES medium, contrarily it resulted with a slower release. This could be not only the aromatic rings reported to slow down the release of ionic species from the ion exchangers, but also the result of the counter ions inside the medium. The release from all ion exchangers were fitted to either Fickian or non-Fickian diffusion by fitting to Higuchi or zero order release kinetics and the main parameter controlling the release was found as the ion exchanger, especially in pH 6.8 HEPES media.

AUTHOR CONTRIBUTIONS

Concept: Ö.İ.; Design: Ö.İ.; Control: Ö.İ.; Sources: Ö.İ.; Materials: Ö.İ.; Data Collection and/or Processing: Ö.İ.; Analysis and/or Interpretation: Ö.İ.; Literature Review: Ö.İ.; Manuscript Writing: Ö.İ.; Critical Review: Ö.İ.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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