FABAD Farm. Bil. Der.
17, 33 - 38, 1992

FABAD J. Pharm. Sci.
17, 33 - 38, 1992

BIOADHESIVE POTENTIAL OF BIOADHESIVE TABLETS

Ayla GÜRSOY (*1)
İnci SOHTORİK (*)
Nurseli UYANIK (**)

Summary: Bioadhesive tablet formulations were prepared from polyacrylic acid (PAA) and /or carboxymethyl cellulose (CMC) or tragacanth and were tested for their bioadhesiveness to bovine nasal, buccal and vaginal mucous membranes and to sodium alginate gel. Of the different mucous membranes the buccal membrane showed the maximum detachment force which occured for the F-PA and F-CA tablets. The detachment force varied almost linearly with the bioadhesive material content. However tablets containing tragacanth did not show a significant bioadhesion difference between the mucous membranes tested and their bioadhesiveness was less than PAA and CMC containing tablets. The tablets showed a weak bioadhesion to the sodium alginate gel (I) compared to other mucous membranes.

When bioadhesive tablets were prepared by blending 50 % drug (zinc sulphate) with PAA or CMC and tested for their bioadhesiveness to sodium alginate gels (prepared from two different viscosity grades), it was found that blending with 50 % drug weakened the bioadhesiveness of both PAA and CMC. Furthermore, the adhesive capacity of the sodium alginate did not change with its viscosity.

BİYOADHESİF TABLETLERİN BİYOADHESİF GÜCÜ

Özet: Poliakrilik asit(PPA) ve/veya karboksimetil selüloz (CMC) veya kitre zamkı içeren tablet formülasyonları hazırlanarak bunların öküz burun, yanak ve vajinal mukus membranlarına ve sodyum aljinat jeline yapışma gücü araştırıldı. Değişik mukus membranlar içinde bukal membran maksimum kopma gücünü F-PA ve F-CA tabletlerine karşı gösterdi. Kopma gücünün değişimi biyoadhesif madde miktarı ile oldukça paralel bulundu. Ancak kitre içeren tabletler mukus membranlar arası biyoadheziyon farkı göstermedi ve biyoadhesiflikleri PAA ve CMC içeren tabletlerden daha az bulundu. Tabletler diğer mukus membranlara göre sodyum aljinat jeline (I) daha zayıf bir biyoadheziyon gösterdiler.

% 50 etken madde (çinko sülfat) ve PAA veya CMC karışımı tabletler hazırlanıp sodyum aljinat jeline (iki farklı viskozite cinsi ile hazırlanmış) karşı biyoadhesif güçleri incelendiğinde % 50 oranında ilaçla karıştırmanın hem PAA hem de CMC için biyoadhesif gücü azalttığı saptandı. Ayrıca, sodyum aljinatın yapışma kapasitesi viskoziteye bağlı değişim göstermedi.

Key words : Bioadhesive tablets, nasal, buccal, vaginal mucous membranes, sodyum alginate gel, PAA, CMC, tragacanth, zinc sulphate

Başvuru Tarihi : 3.6.1991
Kabul Tarihi : 24.10.1991

(1) Correspondence
(*) Marmara Üniversitesi Eczacılık Fakültesi, Farmasötik Teknoloji ABD, İstanbul
(**) İstanbul Teknik Üniversitesi Fen-Edebiyat Fakültesi, Kimya Bölümü, Maslak-İstanbul

INTRODUCTION

Biodhesive polymers have been found useful in extending the duration of contact of drugs with absorbing membranes. The majority of the papers, which have dealt with the different adhesive capacities of various polymers have reported the importance of polymer composition, their glass transition temperature, the type of tissue, the mucus quality and quantity, and the testing conditions on bioadhesion (1-7). The relative adhesiveness of polymers has been estimated using mucous membranes or artificial hydrogels such as gelatin and 1 % alginic acid (8). Generally polymers with a high molecular weight and containing ionizable groups have been noted as the most adhesive. Specifically anionic polyelectrolytes particularly cellulosic and acrylic polymers have been found to be promising bioadhesive substances (4,9). Also tragacanth has been reported as an excellent adhesive (8).

In the present work Avicel PH 102 as a tablet diluent, tablets were prepared from different polymers each of which were added in two different ratios. Their bioadhesiveness to nasal, buccal and vaginal mucous membranes and to sodium alginate gel were investigated. Tablets prepared using ethylcellulose as a nonbioadhesive reference polymer were also investigated. Furthermore, the changes that might occur in tablet bioadhesiveness to sodium alginate gels after the incorporation of a 50 % drug to the bioadhesive tablet formulations were investigated. Zinc sulphate was used as a model drug.

MATERIALS AND METHODS

Tablet formulations were prepared using poly (acrylic acid) (PAA) (Carbopol^R 934, B. F. Goodrich Co., Breckswille, Ohio, USA). Sodium carboxymethyl cellulose (NaCMC, Hercules, Wilmington, De, USA, with viscosity of 430 cps at 25°), ethylcellulose (EC) (EC-N-10, Hercules Wilmington, De, USA), tragacanth (Sigma Chemicals Co. St. Louis, MO, USA), microcrystalline cellulose (Avicel PH 102, F.M.C. Corp. Marcus Philadelphia, Pa, USA) as a diluent. Sodium alginate (I) (Protonal Sf-120 A.S Proton-Drammen, Norwegen, with viscosity of 1 % solution at 20° is 120 cps), sodium alginate (II) (Kelgin HV, Kelco Comp. Clark N.J. Calif. USA with viscosity of 1% solution at 20° is 700 cps), zinc sulphate ($ZnSO_4$ $7H_20$, Merck, Darmstadt, FRG). All other chemicals either reagent or analytical grade were used as received.

For tablet preparation, the materials were sieved and mixed according to the mixtures in Table 1 and Table 3 and compressed directly using a single punch tablet machine (Korsch E.K.O West Berlin) fitted with flat-faced punches.

The force required to separate a bioadhesive tablet from the mucous membrane specimen or sodium alginate gel was measured using a tensile-tester apparatus (Tensilon, UTM II, Toyo Measuring Instruments Co. Ltd. Tokyo, Japan). To adapt the apparatus for the bioadhesive tablet test, two clamps made of stainless steel were constructed, one to hold the tablet and the other, the mucosa. Freshly slaughtered bovine nasal, buccal and vaginal parts were removed and stored at - 30°C. For the experiment a section of mucosa (2 mm thicks) from the above mentioned organs was cut and placed on the lower clamps of the apparatus. Membranes were used without removing the mucus. A tablet was attached to the

upper clamp. Both were glued to the clamps using a liquid cyanoacrylate adhesive. A sample of 10 µl of water was placed on the tablet surface using a Hamilton syringe and the two surfaces were brought into contact. After 10 minutes of contact time under an initial pressure of 4.41 kPa the clamps were placed in the apparatus and the tablet surface was brought into contact with mucous membrane. In order to compare the adhesive capacity of the sodium alginate gel with the mucous membranes, a 1% w/v sodium alginate gel was prepared and used in place of the mucous membrane. For these latter tests the initial application of pressure was omitted. The tension at which the tablet separated from the membrane or sodium alginate gel was taken as the final value which was used to estimate the detachment force of the polymers as calculated in our previous work (6).

RESULTS AND DISCUSSION

The tablet formulations prepared from polymers, tragacanth and Avicel PH 102 are given in Table 1. Two different ratios of each were used.

As is shown in Table 2, when these tablets were investigated for their adhesiveness to nasal, buccal, vaginal mucous membranes and sodium alginate gel (I), except for F-1EA and F-2EA tablets, all of them showed a detachment force which varied with each type of bioadhesive material. The detachment force varied proportionally to the bioadhesive material content. Only in the F-1EA and F-2EA tablets did the polymer content not effect the detachment force and for the sodium alginate gel the force was nil. Since the materials only become adhesive on hydration and since EC is not a polymer which hydrates in contact with water it therefore showed poor adhesiveness.

However tablets containing tragacanth did not show a significant difference in bioadhesion with different mucous

Table 1. Bioadhesive tablet formulations

Tablet Code No.	PAA (wt %)	CMC (wt %)	EC (wt %)	Tragacanth (wt %)	Avicel PH102 (wt %)
F-1PA	15	—	—	—	85
F-2PA	45	—	—	—	55
F-1CA	—	15	—	—	85
F-2CA	—	45	—	—	55
F-1TA	—	—	—	15	85
F-2TA	—	—	—	45	55
F-1EA	—	—	15	—	85
F-2EA	—	—	45	—	55

Table 2. Detachment force (N) between bioadhesive tablet and mucous membrane and sodium alginate gel (I) (mean of 5 ± SD)

Tablet. Code No.	Tablet diameter (mm)	mucous membranes			Na alginate gel (I)
		Nasal	Buccal	Vaginal	
F-1PA	8.71 ± 0.02	0.393 ± 0.083	0.806 ± 0.060	0.433 ± 0.030	0.271 ± 0.045
F-2PA		0.733 ± 0.082	1.277 ± 0.011	0.548 ± 0.060	1.680 ± 0.415
F-1CA	8.76 ± 0.03	0.237 ± 0.045	0.234 ± 0.068	0.271 ± 0.046	0.123 ± 0.017
F-2CA		0.375 ± 0.059	0.746 ± 0.133	0.362 ± 0.031	0.221 ± 0.050
F-1TA	8.74 ± 0.03	0.144 ±0.033	0.170 ± 0.019	0.152 ±0.031	0.057 ± 0.012
F-2TA		0.208 ± 0.035	0.238 ± 0.045	0.220 ± 0.040	0.097 ± 0.015
F-1EA	8.71 ± 0.02	0.139 ± 0.027	0.029 ± 0.028	0.151 ±0.041	0.000
F-2EA		0.147 ± 0.023	0.006 ± 0.009	0.125 ± 0.035	0.000

membranes. Also the tragacanth content of tablets did not significantly effect the bioadhesion force. The bioadhesion values of the tragacanth tablets were less than that of the tablets which contained PAA and CMC. Of different mucous membranes the buccal membrane showed the maximum detachment force and this occurred with F-PA an F-CA tablets. However these tablets showed little difference in adhesiveness between the nasal and vaginal membranes. The difference between the bioadhesive values of these membranes might have been due to the biochemical and reological properties of the mucus as much as to its quantity. There was not a pH difference between the mucous membranes. The pH's of nasal, buccal and vaginal mucous membranes and alginic acid gels were 7.2, 7.5, 7.5 and 6.5 respectively. Therefore differences in pH of the different mucosa cannot be said to be a factor influencing their bioadhesiveness. In the literature there is conflicting results on the effect of pH. According to Lejoyeux et al., (10) pH did not significantly modify the work of adhesion. Yet Park et al., (11) reported that the adhesion force was a function of pH.

The tablets showed a weak bioadhesion to the sodium alginate gel (I) compared to adhesion to other mucous membra-

nes. However bioadhesiveness to the alginate gel (I) varied quite significantly with changes in the bioadhesive material content of the tablets (Table 2).

Tablet formulations containing 50% zinc sulphate (Table 3) were also tested for their adhesiveness to the sodium alginate gels (I, II) which had been prepared from two different viscosity grades of sodium alginate (Table 4).

Although PAA and CMC are good biodhesive materials, blending them with the 50% zinc sulphate was found to weaken their adhesion. Tablets prepared by adding both PAA and CMC (F-IPCZ and F-2PCZ) did not show an obvious bioadhesive difference from the tablets prepared from the individual polymers. Also, the adhesive capacity of the sodium alginate did not change with its viscosity.

Table 3. Bioadhesive tablet formulations containing zinc sulphate

Tablet Code No.	PAA (wt %)	CMC (wt %)	Avicel PH102 (wt %)	$ZnSO_4$ $7H_2O$ (wt %)
F-1PCZ	15	35	—	50
F-2PCZ	40	10	—	50
F1PAZ	15	—	35	50
F-2PAZ	40	—	10	50
F-1CAZ	—	15	35	50
F-2CAZ	—	40	10	50

Table 4. Detachment force (N) of zinc sulphate containing bioadhesive tablets from sodium alginate gels (Mean of 5 ± SD)

Tablet Code No.	Tablet diameter (mm)	Na alginate gel (I)	Na alginate gel (II)
F-1PCZ	10.10±0.02	0.070±0.008	0.050±0.010
F-2PCZ		0.064±0.004	0.052±0.020
F-1PAZ	8.62±0.02	0.038±0.004	0.029±0.006
F-2PAZ		0.046±0.003	0.044±0.005
F-1CAZ	8.62±0.02	0.084±0.002	0.048±0.007
F-2CAZ		0.088±0.006	0.068±0.020

As a conclusion, tablets prepared from PAA gave a better bioadhesion to nasal, buccal, vaginal and also to the sodium alginate gel (I) than CMC containing tablets. Of the mucous membranes the buccal membrane was found to be the most bioadhesive. Under these test conditions tragacanth was not found to be as good a bioadhesive material as PAA and/or CMC. Since it is not always easy and practical to carry out the bioadhesion tests with mucous membranes it has been shown that sodium alginate gels can be used in place of mucous membranes, particularly for the tablet formulations which mainly contain a bioahesive polymer. When the drug content of the bioadhesive tablets was 50% the sodium alginate gels were no longer useful for comparing their bioadhesiveness.

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