

Triamcinolone Acetonide Buccal Bilayered Discs For Treatment of Erosive Oral Lichen Planus: Design and *In vitro* Characterization

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Triamcinolone acetonide (TA) is a glucocorticoid commonly used for the treatment of oral lichen planus (OLP). To avoid extensive first pass metabolism and to prolong the duration of its action with a reduction in dosing frequency, buccal adhesive discs of TA were evaluated. A bilayered bioadhesive buccal dosage disc containing TA was chosen. The discs were prepared by adding a 3:1 combination of chitosan polymer, which has adhesive properties, and hydroxypropyl methylcellulose (HPMC K4M) or Carbopol 934P (C934P). Beta-cyclodextrin (BCD) was used to improve the solubility of the TA. The experiments performed on the discs were radius thickness, homogeneity, surface pH, swelling index (SI) determination, and *in vitro* active ingredient secretion. Based on the study results, the T1 coded formulation containing chitosan and HPMC K4M was determined to be the best, achieving the highest effective active ingredient release and an acceptable level of swelling properties. This indicates that the formulation can be a good alternative to the dosage forms currently used in the topical treatment of OLP.

Key words: Oral lichen planus, Buccal adhesive discs, Triamcinolone acetonide, Chitosan, Carbopol 934P, HPMC K4M, Topical treatment

Erosiv Oral Liken Planus Tedavisi İçin Triamsinolon Asetonid Bukkal Çift Tabakalı Diskler: Hazırlanması ve *In Vitro* Karakterizasyonu

Triamsinolon asetonid (TA), oral liken planus tedavisinde sıklıkla kullanılan bir glukokortikoiddir. İlk geçiş etkisine uğramasını önlemek ve etki süresini uzatarak dozlama sıklığını azaltmak için TA'nın bukkal adhesif diskleri çalışılmıştır. TA içeren biyoadhezif bukkal dozaj şekli olarak çift tabakalı disk formu tercih edilmiştir. Diskler, adhezif özelliğe sahip bir polimer olan kitozan ile hidroksipropilmetil selüloz (HPMC K4M) ve Carbopol 934P'nin 3:1 oranında birlikte kullanımı ile hazırlanmıştır. TA'un çözünürlüğünü artırmaya yardımcı olması için β -siklodekstrinden yararlanılmıştır. Hazırlanan diskler üzerinde; çap-kalınlık, içerik tekdüzeliği, yüzey pH'sı ve şişme indeksi ölçümleri yapılmıştır. Ayrıca; *in vitro* etkin madde salım çalışmaları da gerçekleştirilmiştir. Yapılan çalışmalar sonucunda bulunan veriler değerlendirildiğinde; kitozan ve HPMC K4M içeren T1 kodlu formülasyonun en yüksek etkin madde salımı sağlaması ve Kabul edilebilir düzeyde şişme özelliğine sahip olması nedeni ile en iyi formülasyon olduğuna karar verilmiştir. Bu formülasyon, OLP'nin topikal tedavisinde kullanılan dozaj formlarına iyi bir alternatif olarak değerlendirilebilir.

Anahtar kelimeler: Oral liken planus, Bukkal adhesif disk, Triamsinolon asetonid, Kitozan, Karbopol 934P, HPMC K4M, Topikal tedavi

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INTRODUCTION

Lichen planus is a chronic inflammatory and autoimmune disease that affects cutaneous and mucosal tissues. It is seen in 0.5–2% of the population (1). Oral lichen planus (OLP) is a common form of the disease, which is more resistant to drug therapy (1, 2). OLP has six clinical variants: reticular, papular, plaque-like, erosive, bullous, and atrophic (3). The first three of these variants present with painless, white keratotic lesions usually cured without the need for medication. However, the erosive, bullous, and atrophic forms present with a burning sensation and pain, which affect the quality of life in patients. Furthermore, the atrophic and erosive types have the potential to become malignant (4, 5). Therefore, effective treatment of the disease is necessary (6).

The primary goal in the treatment of OLP today is to reduce the symptoms, extend the lesion-free period, and prevent malignancy (7, 8). Standard therapy includes systemic or topical corticosteroids, which are chosen both for their anti-inflammatory effects and anti-proliferative properties. Drugs with mild, high, or super potencies are chosen based on the severity of the disease (9).

Topical corticosteroids are the drugs of choice in the treatment of mild and moderate cases of OLP. They can be applied to the oral mucosa in the form of gels, ointments, pastes, mouthwashes, and pastilles for inhalation (10). The most common difficulty in the treatment is the inability of the drugs to stay on the mucosa, which in turn reduces the absorption of the drug and extends the treatment period (10). It is, therefore, recommended to mix the drugs in the form of pastes or ointments with equal amounts of Orabase in order to increase their absorption. Apart from these, the most successful application of the drug is obtained through gels. It is recommended that topical corticosteroids can be used three times daily, following meals and once before the bedtime (1, 11). The most commonly used topical corticosteroids are triamcinolone, fluocinonide, and clobetasol, which are all fairly effective (12).

It is well known that systemic corticosteroids should be used cautiously due

to their secondary effects. Although topical applications have lower risks, the corticosteroids have the potential for adverse effects, such as hirsutism and moon face, as well as changes in endogenous cortisol secretion, which results in addiction. Furthermore, corticosteroid-induced local immunosuppression increases the risks for opportunistic infections such as oropharyngeal candidiasis (13). All these effects are related to the dose, potency, and duration of the treatment. Therefore, it is very important to treat the conditions with the right dose of corticosteroids for the required duration, and phasing out the drugs over time following cure (14).

Conventional drugs containing corticosteroids applied to the oral mucosa achieve a high level of drug delivery; however, their duration of action is relatively short (15). The reason for this is the presence of various physiological removal mechanisms in the oral cavity, such as saliva secretion, tongue movement, temperature, and the swallowing reflex (16). The classic dosage typically remains in the mouth for 5–10 minutes and then is rapidly removed from the application area (17). Mucoadhesive/bioadhesive drug delivery systems allow the carrier systems to adhere to the mucosa, thereby increasing the duration that the drug remains in the absorption site and improving the local concentration of the drug by preventing the loss of its active and inactive ingredients in the oral cavity (17, 18). As a result, the buccal membranes are in contact longer with the drug, resulting in a higher degree of active ingredient absorption (15, 16). Furthermore, the buccal region is an appropriate area for the application of adhesive systems due to its flat and immobile surface.

There are several forms of adhesive dosage drugs developed for buccal applications: tablets (19), discs (20), gels (21), sprays (22), solutions (23), patches, and films (24, 25). The solid dosage forms, such as tablets and discs, allow for more regular dosages compared to the other forms and, therefore, are preferred (26). Discs, like tablets, are non-flexible media that are easily produced. On the other hand, discs are thinner compared to tablets and can be produced in any shape,

allowing for a higher degree of patient compliance (27). These properties make discs a superior form to be used as buccal adhesive drugs.

The purpose of this study was to develop bilayered buccal bioadhesive discs containing triamcinolone acetonide (TA) for the topical treatment of OLP. For this purpose, chitosan was chosen as the primary polymer. Next, hydroxypropyl methylcellulose (HPMC K4M) and Carbopol 934P (C934P) were chosen as the secondary polymers. Beta-cyclodextrin (BCD) was used to modify the secretion of active ingredients from the hydrophilic matrix. The experiments performed on the prepared discs were radius thickness and surface pH measurements, swelling index (SI) determination, and *in vitro* active ingredient release experiments.

MATERIALS AND METHODS

Materials

Triamcinolone acetonide was received as a gift sample from İbrahim Ethem Ulagay Pharmaceutical Company (Turkey). Medium molecular weight chitosan (MMW) (viscosity: 200 mPa), Carbopol 934P (C934P), Hydroxypropyl methyl cellulose (HPMC K4M) (4000 mPa.s), β -cyclodextrin (BCD) and magnesium stearate (MgSt) were purchased from Aldrich (Germany), Noveon (USA) and Fluka Biochemika (Japan, Hungary) and Merck (Germany), respectively. All other reagents and materials were of analytical grade.

Preparation of buccal adhesive bilayered discs

The bilayered buccal bioadhesive discs containing TA were prepared by using a direct compression method. The bilayered discs consist of a backing layer that allows for one-way passage of the adhesive layer and active ingredient towards the mucosa. The primary polymer chosen for the adhesive layer was MMW chitosan. The secondary polymer was HPMC K4M or C934P added in a 3:1 ratio (chitosan:polymer). The backing layer consisted of ethyl cellulose (EC). The combinations of the prepared formulations can be seen in Table 1. BCD was added to the disc formulation to improve the solubility of the active ingredient, and MgSt was added as a lubricant. The ingredients making up the adhesive layer, with the exception of the lubricant, were mixed for 10 minutes. MgSt was then added and the entire formulation was mixed for an additional two minutes. The discs were compressed by using 10 mm flat/straight staples. During the compression, the die cavity was filled with the EC (50 mg) that formed the backing layer, and then squeezed with gentle pressure to obtain a uniform surface. Then the adhesive mixture including TA was placed on top. The bilayered discs were then compressed with the hydraulic press for 20 seconds under 200 bar pressure. All disc formulations contained fixed amounts of (3 mg) TA.

Table 1. Compositions of the formulations

Formulation code	Buccal adhesive bilayered disc composition (mg)							Total
	Adhesive layer						Backing layer	
	TA	MMW	HPMC	C934	B-CD	MgSt	EC	
T1	3	45	15	-	-	1	50	114
T2	3	45	15	-	8	1	50	122
T3	3	45	-	15	-	1	50	114
T4	3	45	-	15	8	1	50	122

Characterization of bilayered discs

Content uniformity

To evaluate content uniformity, 10 compressed discs were picked up and powdered. At the next step, an amount equal to a single disc from this powdered material was scaled and mixed with 10 ml methanol. The solution was then filtered and diluted with methanol and analyzed using an ultraviolet and visible (UV-Vis) spectrophotometrically (Thermo Scientific Evolution 201 UV-visible spectrophotometer) at a 235 nm. These experiments were repeated three times.

Radius thickness measurement

The radius and thickness of the compressed discs were measured using calipers. The average and standard deviation values were obtained after measuring 10 discs.

Surface pH of the buccal adhesive bilayered discs

The surface pH of the discs was investigated to determine if any irritation of the oral mucosa occurred. For this purpose, the discs were allowed to swell for 6 hours in 5 ml of a pH 6.8 buffer solution containing 20% propylene glycol (PG, v/v). The electrode of the pH meter was placed against the surface of the swollen discs. The experiment was carried out on five different discs, at room temperature.

Swelling index (SI) studies

Each disc was accurately weighed and placed separately in a 25 ml beaker containing 5 ml of Sorenson's buffer solution (pH 6.8):PG mixture (80:20) at room temperature. At the predetermined time intervals of 1., 2., 3., and 6. hours, the discs were removed,

wiped off with filter paper, and weighed. The SI was calculated by using the following

$$SI = \frac{W_2 - W_1}{W_1} \quad (\text{Equation 1})$$

equation (28):

where SI is the swelling index, W_1 is the initial weight of the discs, and W_2 is the weight of the discs after the particular swelling time interval. Each experiment was performed in triplicate.

In vitro drug release

In vitro drug release studies were performed by static method using glass vessels and thermostatic water baths at 37°C over 6 hours, and stirred at a speed of 200 rpm. The discs were placed in glass vessels containing 50 ml of Sorenson's buffer solution (pH 6.8):PG mixture (80:20, v/v). This mixture of pH 6.8 Sorenson's buffer solution and PG was used to obtain the sink conditions (29). At appropriate time intervals, 2 ml of samples were collected and replaced by an equal volume of a fresh mixture of the buffer solution:PG. The TA content was analyzed by spectrophotometrically. All release studies were performed in triplicate.

Drug release kinetics

Curve fitting was performed using Microsoft Excel, version 2000. The dissolution data where M_t/M_∞ is the fraction of drug released at

$$M_t / M_\infty = kt^n \quad (\text{Equation 2})$$

time t , k is the kinetic constant of the system, and n is the exponent characteristic of the mode transport as seen in Table 2.

Table 2. Analysis of diffusional release mechanism (31)

Diffusional release exponent (n)	Overall solute diffusion mechanism	Time dependence of solute release rate (dM_t/dt)
$n=0.5$	Fickian diffusion	$t^{-0.5}$
$0.5 < n < 1.0$	Anomalous (non-Fickian) diffusion	t^{n-1}
$n=1.0$	Case II transport	Zero-order release
$n > 1.0$	Super Case II transport	t^{n-1}

RESULTS AND DISCUSSION

In this study, adhesive discs containing TA were developed for application to the buccal mucosa during the topical treatment of oral lichen planus. Bilayered discs consisting of chitosan and HPMC K4M/C934P polymers were prepared.

Content uniformity, thickness, and diameter

Thickness-diameter measurements and content uniformity tests were conducted on the discs. These results are shown in Table 3. Based on the findings, the content uniformity of the discs was between 95–98%.

Disc thicknesses ranged between 1.33 ± 0.001 mm and 1.43 ± 0.01 mm. The radii of all discs were 10 mm. The radius and thicknesses of the discs were within appropriate ranges to be applied to oral mucosa.

Table 3. Surface pH, thickness and diameter results of bioadhesive TA buccal discs (Mean \pm Standard Deviation) (n=5)

Code	Surface pH	Thickness (mm)	Diameter (mm)
T1	5.67 \pm 0.17	0.133 \pm 0.001	10
T2	5.50 \pm 0.15	0.134 \pm 0.01	10
T3	5.66 \pm 0.19	0.142 \pm 0.00	10
T4	5.62 \pm 0.12	0.143 \pm 0.01	10

Surface pH

The results given in Table 3 show that the surface pH values of all discs were within the range of 5.50 ± 0.15 and 5.67 ± 0.17 , which were within the acceptable salivary pH range (5.5–7.0). These results indicate that there is no risk of mucosal damage or irritation while administering these formulations on buccal mucosa (32).

Swelling index (SI)

The amount the discs swell when applied to the patient is an important indicator of patient compliance, because the dosage form inside the patient's mouth should not intervene with the daily activities of eating, drinking, or swallowing. In the event of discomfort or interference, patients may cease using the drug and interrupt their ongoing treatment.

The buccal adhesive dosage form should have sufficient swelling ability to adhere to the mucosa and release the active ingredient, but not to the degree of disrupting the patient's comfort. The SI values for the discs can be seen in Figure 1. The values were found between 1.31 and 2.84, in the ranking order of T2 > T3 > T4 > T1. Based on these findings, the formulation coded T2, in which HPMC K4M was used as the secondary polymer and contained BCD, had the greatest amount of swelling. The least amount of swelling was observed in the T1 formulation containing HPMC K4M.

When the prepared discs were compared based on the secondary polymers, the formulation containing C934P absorbed water faster, resulting in the greatest degree of swelling. The reason behind it is that the carboxylic groups in the C934P were ionized resulting in loosened polymer chains, which in turn increase the water absorption and SI value (33).

Figures 1 and 2 show that the BCD had positive effects on the prepared discs. While this effect was not statistically significant on C934P, significant effects are seen in formulations prepared with HPMC K4M. This is thought to be due to the rapid dissolution of CD and acting as a wicking agent, thereby increasing the hydration of the polymer mix (34).

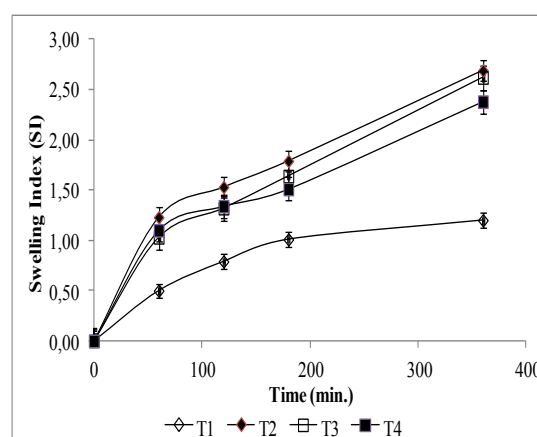


Figure 1. Swelling index profile of bilayered adhesive TA buccal discs

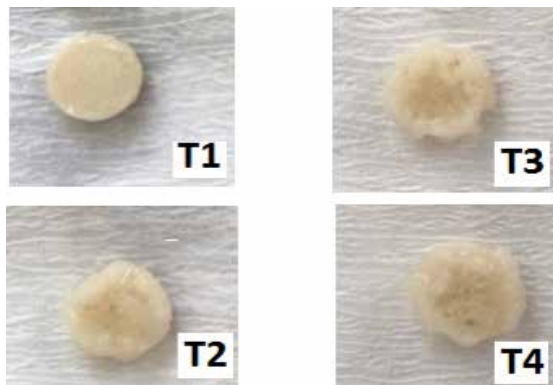


Figure 2. The images of buccal bilayered discs obtained after 6 hours swelling studies.

In vitro drug release

As seen in Figure 3, the active ingredient release order of the formulations, based on the amount of TA released, is $T2 > T4 > T3 > T1$. The highest amount of active ingredient release was achieved in T2, in which HPMC K4M was used as the secondary polymer and contained BCD.

The *in vitro* active ingredient release test revealed no significant difference between the HPMC and C934P formulations as far as the amount of active ingredient release from the discs after six hours. Although C934P has far more hydrophilic properties compared to HPMC K4M, the reason for this lack of significant difference is thought to be the development of complexes between the oppositely charged polymers, C934P and chitosan. In other words, we consider that an intra-polymer complex could be developed between hydroxyl or amino groups of the cationic chitosan and the carboxylic groups of the anionic C934P. This increases the dissolution time of the active ingredient (35).

Furthermore, C934P showed a greater amount of swelling, because it is more hydrophilic compared to HPMC and, therefore, can absorb more water. A greater amount of swelling might have resulted in greater viscosity of the gel layer forming around the discs and increased diffusion distance for the active ingredient. This explains the delayed release of the active ingredient (36).

When the release of TA from the BCD discs was evaluated, a greater amount of TA was

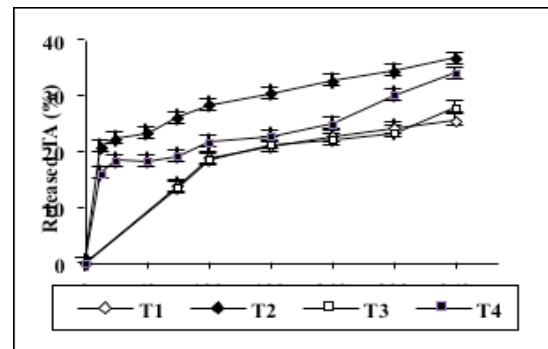


Figure 3. *In vitro* release of TA from bioadhesive buccal discs

released from the formulations containing BCD. Since TA has a low level of solubility in water, a limited amount is dissolved in the hydrated matrix structure. The addition of BCD into the system increases the dissolution rate of the active ingredient in the polymeric gel matrix by developing an in situ complex (34). Furthermore, BCD increases the release of active ingredients by supporting the matrix erosion as a water absorber component. CD is dissolved after coming into contact with water and increases the porosity of the matrix (34). The burst effects that can be seen in Figure 3 in the profiles of formulations containing BCD support this statement. A steadier but controlled release is achieved after the polymeric matrix is hydrated and gelled. Formation of an in situ complex between the active ingredient in the hydrated matrix and CD increases the solubility of TA, resulting in a greater amount of release. Similar findings were reported by other researchers (34).

The *in vitro* release data obtained for exploring the TA release mechanisms from the prepared discs were evaluated using the Korsmeyer-Peppas equation:

$$M_t/M_\infty = Kt^n$$

In this equation, M_t/M_∞ represents the fraction of released active ingredient; k , the release rate constant, n , the diffusional constant characterized by the type of the release mechanism occurring during the dissolution. The n value is calculated by a linear regression of $\log(M_t/M_\infty)$ against $\log(t)$.

For non-Fickian release, the value of n falls between 0.5 and 1.0; while in the case of

Fickian diffusion, $n = 0.5$; for zero order release (case II), $n = 1$; and for (super case II), $n > 1$. The obtained values of n (diffusional exponent), and r^2 (correlation coefficient) are depicted in Table 4.

The kinetic evaluations revealed that the release from all formulations, except for T2, was consistent with Higuchi kinetics. In the T2 coded disc, in which HPMC K4M was used as the secondary polymer with BCD, the release was achieved with zero order kinetics. Similar results were obtained in other studies in which BCD was added to formulations in order to modify the release of active ingredients (37). In the present study, the increased solubility of active ingredients

following the development of an inclusion complex with CD resulted in first order kinetics, whereas the physical mixture was consistent with zero order kinetics.

All formulations exhibited non-Fickian behaviour when evaluated with the Korsmeyer-Peppas equation ($n > 0.5$) (Table 4). In other words, active ingredient release occurred by both diffusion controlled and erosion controlled manners. This means that the release of TA from the prepared discs was controlled first by the swelling of the polymer, then the diffusion of the active ingredient from the swollen polymer, and finally, the steady erosion of polymer (38).

Table 4. Release exponents, n , correlation coefficients, r^2 , calculated from dissolution data of buccal adhesive bilayered disks

Kinetics	Release components	Formulations			
		T1	T2	T3	T4
Zero Order	n	0.1611	21.578	1.088	12.053
	m	0.00456	0.04471	0.0844	0.0621
	r^2	0.7129	0.9729	0.8595	0.736
	RMS	0.403	0.028	0.164	0.359
First Order	n	0.1668	1.031	1.389	0.9353
	m	0.004513	0.00197	0.0817	0.002012
	r^2	0.7016	0.2866	0.8332	0.3395
	RMS	0.425	2.49	0.201	1.95
Higuchi	n	-4.83	9.966	-5.163	6.608
	m	1.72	1.536	1.76	1.378
	r^2	0.8816	0.8311	0.892	0.8655
	RMS	0.134	0.2031	0.121	0.155
Korsmeyer-Peppas	n	-0.5103	0.3286	-0.5143	0.2828
	m	0.7218	0.5402	0.7242	0.5165
	r^2	0.6732	0.8157	0.6755	0.839
	RMS	0.486	0.226	0.48	0.192

CONCLUSION

The oral bioadhesive system plays an important role in the treatment of oral lichen planus. In this study, a well-tolerated alternative system was intended to be produced in order to eliminate disadvantages, such as difficulty applying Orabase and low patient tolerance. In conclusion, the data

obtained in this study indicate that combining chitosan and HPMC can be used as a vehicle for the delivery of an active substance to the oral cavity.

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