Zagazig J. Pharm. Sci., June 2006
Vol. 15, No. 1, pp. 9-15

ISSN 1110-5089

THE EFFECT OF PERMEATION ENHANCERS ON THE PHYSICAL CHARACTERS AND PERMEATION PARAMETERS OF BUCCOADHESIVE CHLORPHENIRAMINE MALEATE TABLETS

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ABSTRACT

The buccoadhesive tablets of Chlorpheniramine Maleate (CPM) were prepared using bioadhesive polymers as sodium carboxymethyl cellulose (NaCMC), sodium alginate, hydroxyethyl cellulose (HEC), and hydroxypropylmethyl cellulose (HPMC) in different drug to polymer ratios. The CPM buccoadhesive tablet formulae were subjected to in-vitro permeation studies at pH 6.8 (pH of the buccal medium) using chicken pouch membrane. The effect of permeation enhancers, namely, menthol, sodium lauryl sulphate and sodium salicylate as 5% concentrations, on the in-vitro permeation of CPM from buccoadhesive tablet formulae were studied. The permeation parameters like permeability coefficient (P, cm/hr), diffusion coefficient (D, cm^2/hr) and the enhancement factor (EF) were calculated according to Fick's first law of diffusion. The quality control tests like, disintegration, hardness, friability and weight uniformity were done and the results were compared before and after the addition of permeation enhancers, using analysis of variance test (ANOVA). It was concluded that the permeation enhancing effect of menthol 5% on CPM permeation from all the buccoadhesive tablet formulae is promising, since the conditions applied experimentally in this work mimic to a large extent that presence in the buccal region could reflect the drug behavior towards human buccal membrane.

INTRODUCTION

The oral cavity is an attractive site for drug delivery due to ease of administration, fast drug release and avoidance of possible drug degradation in gastrointestinal tract and first-pass metabolism. Buccal drug delivery specifically refers to the delivery of drugs within/through buccal mucosa to affect local/systemic pharmacological actions[1].

The mouth is lined with a mucous membrane and among the least known of its functions is its capability of serving as a site for the absorption of drugs. In general, drugs penetrate the mucous membrane by simple diffusion and are carried in the blood, which richly supplies the salivary glands and their ducts, into the systemic circulation via the jugular vein[1].

However, inherent limitations, including short residence time, small absorption area and barrier property of the buccal mucosa, are challenges to buccal drug delivery. Buccal penetration enhancers are capable of decreasing penetration barrier of buccal mucosa by increasing cell membrane fluidity, extracting the structural intercellular and/or intracellular lipids, altering cellular proteins, or altering mucus structure and rheology[1]. Various penetration enhancers were studied by others[2-5].

CPM, used in treatment of various allergic conditions, has a hepatic metabolism which can lead to a dramatic reduction in the amount of drug available systemically from a given peroral dose but is avoided by buccal absorption.

Bioadhesive tablets can adhere to the buccal mucosa, and the drug is released upon hydration of the tablet, forming a hydrogel. Tablets of CPM, consist of bioadhesive polymers like sodium carboxymethyl cellulose (NaCMC), sodium alginate, hydroxyethyl cellulose (HEC), and hydroxypropylmethyl cellulose (HPMC) were used in this study.

The aim of the current work is to study the influence of permeation enhancers on the physical properties and the permeation parameters of CPM buccoadhesieve tablets.

EXPERIMENTAL

Materials

Chlorpheniramine maleate (CPM) and Menthol, Adco, (Egypt). Hydroxypropylmethyl cellulose (HPMC 4000), Sigma, (U.S.A). Hydroxyethyl cellulose (HEC, Tylose H300) and Sodium carboxymethyl cellulose (NaCMC), Memphis, (Egypt). Sodium alginate (Na alg.), SISCO Research Laboratories SRL, (India). Talc, Magnesium stearate, Sodium lauryl sulphate (NaLS), Sodium salicylate (Na salicylate), Potassium dihydrogen phosphate and Disodium hydrogen phosphate, ADWIC, (Egypt). Avicel (Nf 18/USP23 M 101), Tong Sing Chemicals Co., (China).

Equipment

Magnetic stirrer, Thermolyne Corporation, Dubuque lowa, (U.S.A). An electric Balance, Mettler AJ100, (Switzerland). Spectrophotometer, Jenway Ltd, Model 6105 UV/V is Felsted, (United Kingdom). Light microscope (XSP-13A), (China). Tablet compression machine, with flat faced single punch with diameter 0.8cm, Erweka, Type EK: 0, Erweka apparatus, Frankfurt, (Germany). Plastic syringe (5 ml), external diameter 1.1 cm, internal diameter 1 cm, Amico, (Egypt). pH meter, Jenway, (United Kingdom). Dial Micrometer, Model 120-1206 (Baty, co., Ltd, Sussex), (England). InStat computer program test, soft ware Ralf Stohlman.

Methodology

I) Preparation of CPM bioadhesive tablet

a) CPM bioadhesive tablets without enhancer

Table (1) shows the composition of CPM tablets using different bioadhesive polymers, each tablet weighing 144 mg and containing 24 mg of CPM. Polymers (HPMC 4000, HEC, NaCMC, Na alg.), Avicel PH-101, magnesium stearate, talc and the drug were weighed, mixed using mortar and a pestle, and tableted by direct compression to produce five formulae.

Table (1): Composition of CPM tablets using different bioadhesive polymers

Content	Weight (mg) per tablet				
	*FNa alg	**FNaCMC	***FHEC	****FHPMC/ NaCMC	****FHEC/ NaCMC
Drug (D)	24	24	24	24	24
Polymer (P)	7.2	21.6	43.2	21.6	21.6
Avicel PH101	111.36	96.96	75.36	96.96	96.96
Mg stearate	0.72	0.72	0.72	0.72	0.72
Talc	0.72	0.72	0.72	0.72	0.72
Total	144	144	144	144	144

F* drug : polymer (1:0.3). F** drug : polymer (1:0.9). F*** drug : polymer (1:1.8). F**** drug : polymer (1:0.9) in polymer/polymer ratio 1:1

b) CPM bioadhesive tablets with different enhancers

The CPM buccoadhesive tablet formulae were prepared as previously, with the addition of 5% of each enhancer [menthol, sodium lauryl sulphate (NaLS) and sodium salicylate (Na salicylate)][9-11]

II) Quality control studies

The prepared CPM buccoadhesive tablets were evaluated for uniformity of weight, hardness, friability and disintegration with/without permeation enhancers. Mean values, and the standard deviations were calculated[10]

III) Permeation Studies

a) Tissue preparation

Fresh chicken pouch membranes of uniform thickness, devoid of fatty tissue materials, were used for this study. To ensure that the epithelium had separated from the underlying connective tissue and had no pores, the tissues were examined with the light microscope[10b]

b) In-Vitro Permeation of CPM through Chicken Pouch Membrane

The permeation of CPM through chicken buccal membrane was carried out by using a simplified assembled diffusion cell, as shown in figure (1). Chicken buccal membrane was stretched around the cut side of the plastic syringe with an effective permeation area of 0.79 cm^2. Each tablet was pressed on the mucosa of chicken buccal membrane for 30 seconds; half ml of phosphate buffer pH 6.8 was added to the donor chamber. The temperature of the buffer solution pH 6.8 in the receptor was maintained at 37±0.5°C, and it was stirred magnetically at 100 r.p.m. Samples withdrawn from the receptor medium at 0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4 hrs,[11] were subjected to spectrophotometric analysis at λ_{max} of 260 nm.

The permeability of CPM was evaluated before and after inclusion of permeation enhancers in the different tablet formulae.

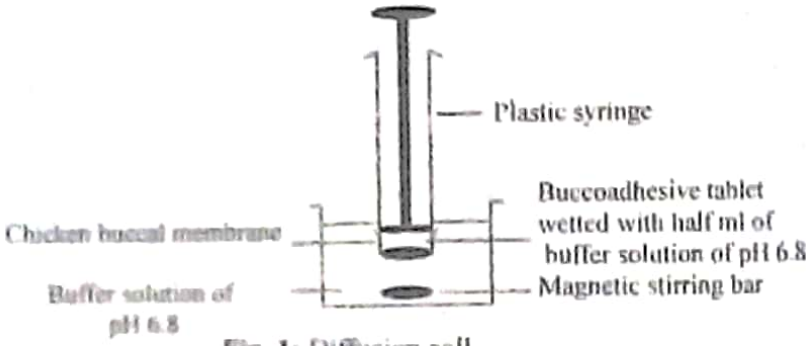

Fig. 1: Diffusion cell.

RESULTS AND DISCUSSION

FNaCMC, FNa alg., FHEC, FHPMC/NaCMC and FHEC/NaCMC have been chosen from previous sytudy[12], and showed optimum results regarding in-vitro release rates, bioadhesive force, swelling index and microenvironment pH, were subjected to permeation studies as in the current work.

Quality control tests

The prepared CPM buccoadhesive tablets were evaluated for uniformity of weight, hardness, friability and disintegration before and after the addition of permeation enhancers. Mean values, and the standard deviations were calculated as shown in table (2).

It was found that all the investigated tablets formulae are still complied with the US Pharmacopoeial[13] requirements, regarding weight uniformity and friability.

The disintegration time of tablets of formulae FNaCMC, FHPMC/NaCMC did not affect by the incorporation of permeation enhancers as they swelled rather than disintegrated. While FNa alg, FHEC, FHEC/NaCMC acquired faster disintegration in the presence of permeation enhancers. These results may be due to the higher water absorption and swelling properties of FNaCMC and FMPMC relative to FNa alg and FHEC.

The quality control test values were treated using analysis of variance which performed on different formulae with / without enhancers. Post ANOVA test was performed according to Tukey-Kramer multiple comparisons using the InStat computer program test. The results are shown in table (2).

In-vitro permeation of CPM through chicken pouch membrane with/without enhancers

Before a buccal drug delivery system can be formulated, buccal absorption/permeation studies must be conducted to determine the feasibility of this route of administration for the candidate drug.

Animal mucosa of rat, chicken, hamster, rabbit, dog, monkey and pig have been used in other buccal drug absorption or permeation studies[14-18]. Freshly slaughtered and conditioned chicken pouch membrane was used in this study because of its availability and suitable consistency of the tissue.

Treating the in-vitro permeation data in accordance with fick's first law of diffusion[17,18], the statistically treated kinetic parameter (b), is used for the determination of the diffusion coefficient D (cm^2/hr) of the drug through chicken pouch membrane, according to the following equation;-

$$J_{ss} = (dQ/dt)_{ss}/A = PC_o = DC_o/h$$

J_{ss} = is the steady state flux of CPM when diffuses through a unit area of a membrane ($mg/cm^2/hr$), and is represented by the slope of the linear regression plot of the amount of CPM penetrated per unit area versus time

$(dQ/dt)_{ss}$ = is the amount of the drug permeated per unit time ($mg\ hr^{-1}$).

A = the surface area of diffusion (0.79 cm^2).

D = is the diffusion coefficient of the drug (cm^2/hr).

P = is the permeability coefficient ($cm\ hr^{-1}$).

C_o = is the initial drug concentration in the donor phase ($48\ mg/cm^3$).

h = is the thickness of the membrane (70 µm i.e., 0.007 cm).

Figures (2-5) showed the amount of CPM permeated per unit surface area from different formulae with/without permeation enhancers plotted versus time. All curves are characterized by an initial high flux, without any lag time, a prompt transport of drug was observed. After 30 min., a steady state flux was reached as represented by the linear part of the permeation profile. The linear part of all curves was used for the determination of the steady state flux (J_{ss}), the permeability coefficient (P) and other concerned parameters.

The oral mucosa represents a barrier to drug permeation and is closer to the skin rather than to the gut in its permeability characteristics. The rate of drug transfer across biological membranes may be enhanced in two major ways. The first is by modification of the physicochemical properties of the drug to optimize membrane/vehicle partition coefficient, the second way involves interaction with the components of the biological membrane to increase its permeability[19].

Because there is little information available on oral mucosal absorption enhancement and no buccal products that contain, these agents are available in the market, an attempt was made to increase the degree of permeation of CPM from different formulae. The permeation enhancers, like 5% menthol, 5% NaLS and 5% Na salicylate have been incorporated separately in the selected formulae.

The efficacy of the different enhancers was determined by comparing the permeability of CPM in the presence or absence of enhancer. It was defined as the enhancement factor (EF) which was calculated using the following equation[15,20];-

$$EF = P\ (enhanced) / P\ (control)$$

Where:

P (enhanced) = permeability coefficient obtained for tablets containing enhancer.

P (control) = permeability coefficient obtained for tablets without enhancer.

As shown in table (3) regarding the enhancement factor parameter (EF) since menthol has maximum EF between all other enhancers, it enhances the permeation of CPM from all formulae through chicken buccal membrane. On the contrary, NaLS and Na salicylate caused no enhancement of drug permeation but they suppressed the permeation of CPM from FNa alg.1, FHEC3 (while NaLS only caused supression of the permeation of CPM from FHEC/NaCMC). These results were confirmed by statistical studies. One way analysis of variance between the EF values of the three enhancers with different formulae, Post ANOVA test was performed according to Tukey- Kramer multiple comparisons using the InStat computer program test (Fig. 6).

Histograms of EF for penetration enhancing activity of menthol, NaLS and Na salicylate are shown in figure (6).

Enhancement resulting from the presence of sodium lauryl sulphate and sodium salicylate was negligible. These results are in accordance with Murthy et al.[21].

Menthol is known to form eutectic mixtures with certain compounds[22,23]. A major benefit of using menthol as permeation enhancer is its safety profile[24]. Furthermore, because of the pleasant taste associated with menthol and its ability to decrease the bitterness of CPM, so its use in a buccal delivery may increase patient acceptability

Table (2): Physical properties of CPM buccoadhesive tablets with/without enhancers

Formula	With/without enhancer	Average weight (mg) ± SD	Friability % (w/w) ± SD	Hardness (kg)±SD	Disintegration time(min)±SD
FNaCMC	without enhancer (control)	144.46±0.30	0.115±0.04	4.70±0.38	swell
	with 5% menthol	149.40±1.14[a]	0.137±0.12	3.69±2.00	swell
	with 5% Na Sal	152±1.40[a]	0.764±0.16[a,b]	2.26±1.20	swell
	with 5% Na LS	152.8±2.40[a]	0.982±0.19[a,b]	2.78±1.00	swell
FNa alg	without enhancer	147.66±2.10	0.090±0.04	2.34±0.03	10
	with 5% menthol	148.98±2.90	0.278±0.03[a]	4.67±1.70	8
	with 5% Na Sal	153±1.00[a]	0.456±0.11[a,b]	3.41±2.10	1
	with 5% Na LS	152.6±0.54[a]	0.345±0.06[a]	3.30±1.50	1
FHEC	without enhancer	147.6±2.80	0.469±0.11	2.47±0.04	swell
	with 5% menthol	149.9±0.60	0.501±0.21	2.7±0.60	15
	with 5% Na Sal	149.24±0.80	0.998±0.09[a,b]	1.3±1.20	15
	with 5% Na LS	153.32±0.83[a,c]	0.749±0.16	1.74±0.60	15
FHPMC/NaCMC	without enhancer	145.44±4.40	0.228±0.04	4.6±0.27	swell
	with 5% menthol	152.6±1.34[a]	0.901±0.62	4.48±1.50	swell
	with 5% Na Sal	152.4±1.14[a]	0.971±0.08	2.19±0.60	swell
	with 5% Na LS	152.8±0.80[a]	0.271±0.07	2.44±1.00	Swell
FHEC/NaCMC	without enhancer	145.42±3.20	0.206±0.12	4.49±0.27	Swell
	with 5% menthol	149.8±0.90	0.862±0.32[a]	3.48±2.10	15
	with 5% Na Sal	152.2±1.09[a]	0.890±0.06[a]	2.15±1.50	10
	with 5% Na LS	152.4±0.90[a]	0.090±0.09[b,c]	2.48±0.60	15

a, b and c : are significant different from control, menthol, sodium salicylate and sodium lauryl sulphate containing formulae respectively, using one way ANOVA followed by Turkey Kramer as post ANOVA test for multiple comparison at P<0.05

Table (3): Permeation parameters of CPM from different formulae with/without enhancer

Formula	With/without enhancer	R	Intercept (a)	$D\times10^{-4}$ cm^2/hr	J_{ss} $mg/cm^2.hr$	P cm/hr	EF
FNaCMC	without enhancer	0.978	2.442	1.132	0.776	0.016	-
	with 5% menthol	0.991	2.176	1.436	0.983	0.205	1.27
	with 5% Na salisylate	0.992	1.451	0.852	0.584	0.012	0.75
	with 5% Na LS	0.986	1.903	1.132	0.776	0.016	1.00
FNa alg	without enhancer	0.975	2.404	2.457	1.685	0.035	-
	with 5% menthol	0.992	2.526	2.740	1.879	0.039	1.12
	with 5% Na salisylate	0.992	0.855	1.657	1.136	0.024	0.67
	with 5% Na LS	0.997	1.291	1.230	0.844	0.018	0.50
FHEC	without enhancer	0.962	3.068	1.808	1.240	0.026	-
	with 6% menthol	0.997	2.284	1.555	1.066	0.022	0.86
	with 5% Na salisylate	0.977	2.977	1.025	0.703	0.015	0.57
	with 5% Na LS	0.993	1.312	1.105	0.758	0.016	0.61

Table (3): *continued*

FHPMC/NaCMC	without enhancer	0.961	2.121	1.602	1.099	0.023	-
	with 5% menthol	0.997	1.771	1.419	0.973	0.020	0.89
	with 5% Na salisylate	0.987	1.741	1.451	0.995	0.021	0.91
	with 5% Na LS	0.996	0.706	1.295	0.888	0.019	0.81
FHEC/NaCMC	without enhancer	0.997	2.201	1.497	1.026	0.021	-
	with 5% menthol	0.993	2.008	1.770	1.214	0.025	1.18
	with 5% Na salisylate	0.998	1.583	1.496	1.026	0.021	1.00
	with 5% Na LS	0.987	1.232	0.940	0.645	0.013	0.63

D is the diffusion coefficient. J_{ss} is the permeation rate constant.
P is the permeability coefficient. EF is the enhancement factor

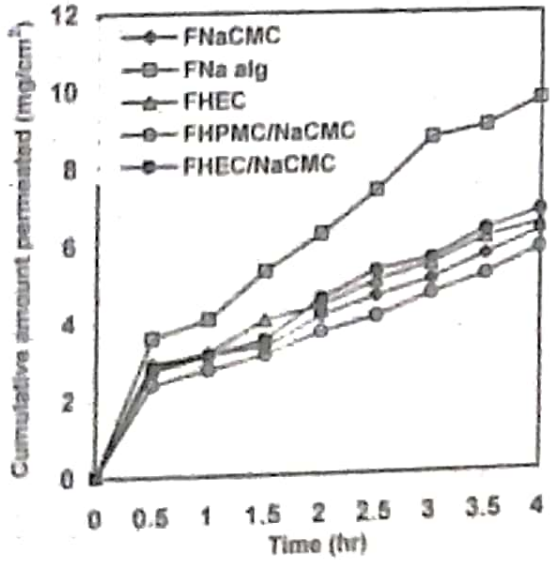

Fig. (3): Effect of 5% menthol on the in-vitro permeation profile of CPM from different formulae through chicken pouch membrane.

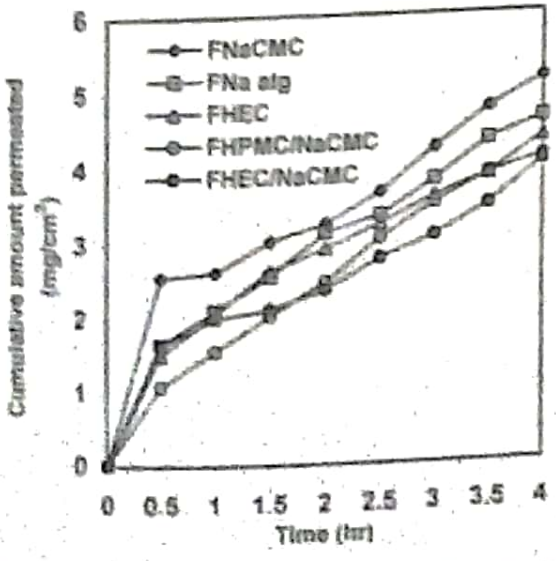

Fig. (4): Effect of 5% NaLS on the in-vitro permeation profile of CPM from different formulae through chicken pouch membrane

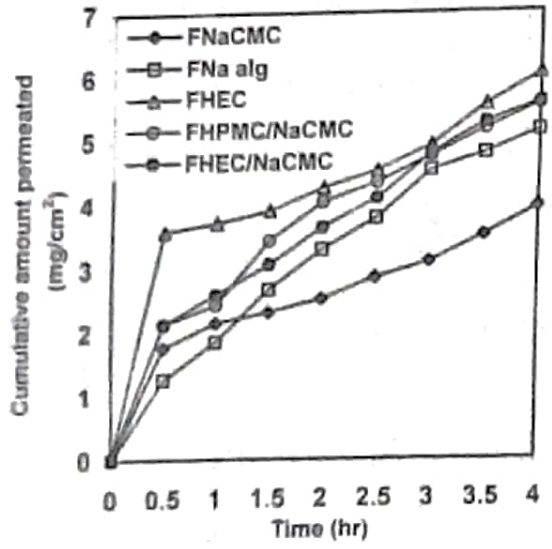

Fig. (5): Effect of 5%Na salicylate on the in-vitro permeation profile of CPM from different formulae through chicken pouch membrane.

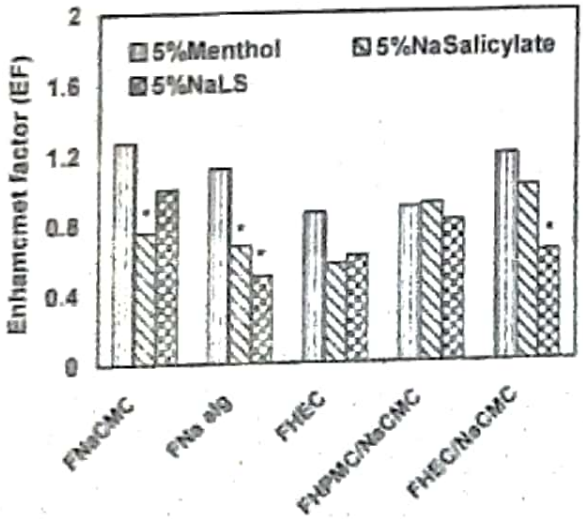

Fig. (6): Histogram of the penetration enhancing activity of the different enhancers on the different formulae
* Significant different with menthol at $p<0.05$

Conclusion:

It was concluded that the permeation enhancing effect of menthol 5% on CPM permeation from the buccoadhesive tablet formulae is promising, since the conditions applied experimentally in this work mimic to a large extent that presence in the buccal region, could reflect the drug behavior towards human buccal membrane.

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Received: Feb. 04, 2006
Accepted: April 11, 2006

Zagazig J. Pharm. Sci., June 2006
Vol. 15, No. 1, pp. 9-15

دراسة تأثير محزات النفاذية علي الخواص الطبيعية وثوابت النفاذية لأقراص ماليات الكلورفينرامين الشدقية اللاصقة

علاء الدين علي قاسم - منها عبد الحميد مرزوق- أمل أبو العينين عمار- غادة حنفي العسيلي

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تشمل الدراسة تحضير بعض الأقراص الشدقية اللاصقة لعقار ماليات الكلورفينرامين والتى تحتوى على (صوديوم كاربوكسى ميثيل سيليلوز, ألجينات صوديوم, هيدروكسى إيثيل سيليلوز, خليط من صوديوم كاربوكسى ميثيل سيليلوز وهيدروكسى إيثيل سيليلوز, خليط من صوديوم كاربوكسى ميثيل سيليلوز وهيدروكسى بروبيل ميثيل سيليلوز ٤٠٠٠).
وقد تم دراسة تأثير محفزات النفاذية (منتول ٥%, لاوريل سلفات الصوديوم ٥%, ساليسلات الصوديوم ٥%) على كل من الخواص الطبيعية مثل زمن التفتت ، درجة الصلابة، الهشوشة و تماثل الوزن بالاضافة لدراسة معدل النفاذية والانتشار لعقار ماليات الكلورفينرامين(من خلال الغشاء المبطن لفم الدجاج) من الصيغ المحضرة للاقراص الشدقية اللاصقة وذلك بتطبيق قانون فيكس الأول لدراسة الانتشار.

وقد تم تقييم النتائج احصائيا باستخدام اختبارات ANOVA عند احتمالات أقل من 0.05 .

قد وجد ان نتائج استخدام منتول ٥% كمحفز للنفاذية فى معظم الأقراص الشدقية اللاصقة فى ظروف مماثلة للغشاء الشدقي الادمي تعتبر مبشرة .