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FORMULATION AND EVALUATION OF BUCCO-ADHESIVE NATAMYCIN TABLET

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تم تحضير أقراص متأكلة لها خاصية الالتصاق بالتجويف الفمى وذلك من أجل التوصيل الموضعى لعقار الناتاميسين فى التجويف الفمى بطريقة الكبس المباشر وذلك باستخدام بولمرات مختلفة لها خاصية الالتصاق الحيوى وصواغات قابلة للذوبان فى الماء مثل المانيتول وعديد الايثيلين جليكول ٦٠٠٠. تم عمل دراسات أولية باستخدام تقنية المسح الحرارى التفاضلى والاشعة تحت الحمراء وذلك للتأكد من عدم وجود أى تفاعلات بين العقار والمواد المستخدمة. تم تقييم الاقراص المحضرة من حيث تجانس محتواها للعقار ، الهشاشية ، الصلابة ، معامل الانتفاخ والاس الهيدروجينى السطحى. وجد من الدراسة أن قوة الالتصاق الحيوى الخارجية وخواص انطلاق العقار تعتمد على نوع البولمر المستخدم وأيضا مكونات الاقراص. تأكد من الدراسات الحيوية أن الاقراص المحضرة التى لا تحتوى على العقار مناسبة بدرجة كافية ولا تسبب أى التهابات وذات طعم مقبول أثناء فترة الدراسة. تم تأكل الاقراص المحضرة بالتجويف الفمى بالكامل غير تاركة أى أجزاء تحتاج للإزالة. أيضا من الدراسات الحيوية لم يسجل أى متطوع علامات جفاف بالفم ولا زيادة فى افراز اللعاب ولا تغيير قوامى فى مكان القرص. الأقراص المحضرة كانت قادرة على أن تحافظ على تركيز العقار فى اللعاب فوق أقل تركيز يمنع نمو الكانديدا لمدة تصل إلى ٦ ساعات.

Bucco-adhesive erodible tablets for local delivery of natamycin (NTM) to the oral cavity were prepared by the direct compression method using different bio-adhesive polymers and soluble excipients like mannitol and polyethylene glycol 6000. Preformulation studies were carried out using DSC and IR techniques to emphasize that there is no interaction between drug and carrier systems. The tablets were evaluated for drug content uniformity, friability, hardness, swelling index and surface pH. The in vitro bio-adhesive strength and release characteristics were found to be a function of the type of the polymer and also the total composition of the tablets. In vivo evaluation of placebo bucco-adhesive tablets revealed adequate comfort, taste and non-irritancy during the period of the study. The bucco-adhesive tablets eroded completely leaving no exhausting device to be removed. None of the volunteers reported severe dry mouth, severe salivation or heaviness at the place of attachment. The selected formulation was able to maintain the salivary concentration of NTM above the MIC against Candida albicans for up to 6 hr.

INTRODUCTION

Oral candidiasis is an opportunistic fungal disease of the tongue and oral mucosa caused most often by *Candida albicans*, it is highly prevalent in a specific group of patients including AIDS patients.[1]

In recent years, significant interest has been shown in the development of bio-adhesive dosage forms for the delivery of drugs to the buccal cavity for the treatment of different diseases.[2-12]

Bucco-adhesive dosage forms offer an attractive pathway for local drug delivery to the buccal cavity because bio-adhesive polymers, as components of drug delivery systems, enable formulations to adhere to mucosal surfaces and thus facilitate controlled drug delivery to defined sites in the buccal cavity.[13,14] It was found that the bio-adhesive dosage forms are superior to

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the conventional dosage forms in controlling the drug delivery and improving the patient compliance.

Natamycin (pimaricin) is polyenes antifungal compound which is effective against a broad variety of fungi, yeasts, some protozoa and some algae.[15]

The aim of the present study was to describe the development and the characterization of a bucco-adhesive tablets for treatment of oral candidiasis.

MATERIALS

Natamycin (NTM) was a gift sample from Yamanouchi Europe B.V., Netherlands; carbopol 934p (cp934p) from B.F. Goodrich, Cleveland, USA; hydroxypropyl methyl cellulsoe (HPMC) from Morgan Chemical Co., Egypt; sodium carboxymethyl cellulose (NaCMC) from Arabic Laboratory Equipment Co., Egypt; Guar gum (GG) from Sigma Chemical Co., Germany; polyethylene glycol 6000 (PEG 6000) from Ubichem, Ltd. And Mannitol BP80 from Elgomhouria Co., Egypt. All other chemicals used were of analytical reagent grade.

METHODS

Preformulation studies

Differential scanning calorimetry (DSC)

The DSC patterns were carried out with Shimadzu Model DSC-50 (Kyoto, Japan). The measurements were done using liquid sample pans at scanning speed of 10°/min under nitrogen stream at flow rate of 40 ml/min from 30° to 300°. Sample weight was about 6.0 mg.

Infrared (IR) absorption spectroscopy

The IR spectra were carried out with Shimadzu IR-470 using KBr disk method. The disks were compressed at a pressure of 6 tonnes/cm^2 using Shimdazu SSP-10A IR compression machine.

Preparation of bucco-adhesive tablets

Bucco-adhesive tablets were fabricated by the direct compression method using the formula shown in Tables 1 and 2. All ingredients of the tablets were pressed through a No. 100 sieve and were mixed by trituration in a glass morter with pestle to obtain uniform mixing. The mixture (200 mg) was then compressed using a 13 mm diameter die on a hydraulic press (Carver Inc., USA) using a compression force of 3 tones, and compression time of 30 sec. The tablets were 1.0-1.2 mm thick depending upon the polymer combination used. Placebo tablets were also prepared as above with a total weight of 190 mg.

Table 1: Composition of various bucco-adhesive tablets.

	Weight in mg of		
Ingredints	A-1	A-2	A-3
Natamycin	10	10	10
HPMC	95	90	85
CP-934p	05	10	15
Mannitol	50	50	50
PEG 6000	40	40	40

Table 2: Composition of various bucco-adhesive tablets.

Ingredients	Weight in mg of				
	X-1	X-2	X-3	X-4	X-5
Natamycin	10	10	10	10	10
Polymer	20	60	100	100	140
Mannitol	90	90	90	50	30
PEG 6000	80	40	-	40	20

Formula code (x) polymer : B, Guar gum ; C , Sodium carboxy methyl cellulose; D , Hydroxy propyl methyl cellulose ; E , Sodium alginate.

Evaluation of bucco-adhesive tablets

Weight uniformity

The weight of each 10 randomly selected tablets was determined by placing the sample on an electronic balance; the average weight of each batch was calculated.

Tablet friability

The friability of 10 randomly selected tablets was estimated using Erweka friabilator (GmbH, Germany).

Tablet hardness

For each formulation, 10 randomly selected tablets were examined using Erweka Hardness Tester, type TAB, (GmbH, Germany).

Drug content uniformity

For each formulation, 5 randomly selected tablets were under investigation. Each tablet was weighed accurately, powdered and transferred into a 50-ml volumetric flask containing 30 ml of methanol and was stirred continously on a magnetic stirrer. The volume was made up to 50 ml with methanol and absorbance was measured spectrophotometrically (Shimdazu, Tokyo, Japan) at 303 nm. The concentration was calculated from calibration curve.

Swelling studies of bucco-adhesive tablets

The swelling index of the tablets was determined. Three tablets were weighed (W_1) and immersed in pH 6.8 phosphate buffer solution maintained at 37°. After 1 hr, the tablets were removed and weight (W_2) was determined. The normalized swollen value/initial value ratios (W_2/W_1) were calculated.

Surface pH of the tablets

The surface pH of tablets was determined to evaluate the possible irritative effects of the formulation on the buccal mucosa. The tablets were left to swell for 2 hr in 1.0 ml of distilled water (pH 5.4±0.05); after this time the surface pH was measured by placing the electrode in contact with the surface of the tablets.[8]

In vitro bio-adhesion test

The bio-adhesive strength of the tablets was measured according to previously published method[16] (Fig. 1) using bovine intestine as a model mucosal membrane. Fresh bovine intestine obtained at slaughter was rapidly frozen to -20°. Before use a circular piece (surface area 2 cm^2) of intestine was cut and brought to room temperature in saline solution, then glued with cyanoacrylate adhesive on the ground surface of a tissue holder made of Plexiglas. Similarly, the tablet was glued to another holder of the same size.

Thereafter, the surface of the mucosal membrane was first blotted with a filter paper and then moistened with 25 µl of phosphate buffer pH 6.8. The two holders with mucosal membrane and tablets were put in contact with each other with uniform and constant pressure for 5 min (preload time) to facilitate adhesion boding. The tissue holder with intestine was allowed to hang on an iron stand with the help of a picce of aluminum wire. A prewieghed lightweight polypropylene bag was attached to the hook on the backside of the formulation holder with a piece of aluminum wire. After a preload time of 5 min, water was added to the polypropylene bag through an intravenous infusion set at a constant rate of one drop/sec until the tablet detached from the tissue. The water collected in the bag was measured and expressed as weight (g) required for detachment. Each experiment was repeated three times.

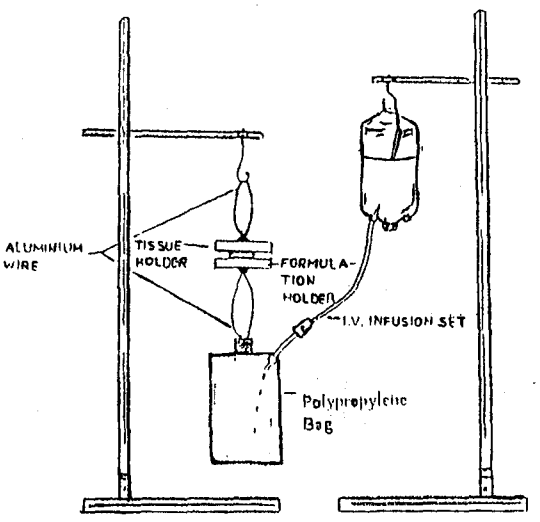

Fig. 1: Modified apparatus for in vitro bioadhesion test.

In vitro drug release studies

The drug release was determined using a dissolution apparatus which, according to USP method II (Paddle), consisted of six polycarbonate vessels placed in a water bath thermostated at 37°±0.5° and stirred at a rate of 50 rpm. Each tablet was fixed at a glass slide so that the drug could be released only from the upper surface and immersed in the vessel containing 250 ml of phosphate buffer pH 6.8 (6.805 g potassium dihydrogen phosphate, 0.896 g sodium hydroxide made up to 1000 ml with distilled water).

Four tablets were examined at the same time. A drug-free tablet, used as blank, was introduced in the fifth vessel. With the aid of pipette, at regular intervals of time, an aliquot of dissolution medium were drawn and the content of natamycin was determined spectrophotometrically at 303 nm. The amount of drug released was calculated on the basis of the standard calibration curve previously constructed.

In vivo evaluation studies

The bucco-adhesion of the drug free tablets was tested in six healthy human volunteers (aged 22-32 years). The tablets was placed between gingiva and cheek and pressed onto mucosa for about 30 sec.[17] Then the tablet and upper lip were moistened with saliva to prevent the sticking of the tablet to the lip.

The duration of mucosal adhesion was the time requied for the complete wash-off of the tablet. The volunteers were asked to record the time of detachment or complete erosion of the tablet, and to monitor for side effects e.g. irritation, hindrance, bad taste, dry mouth, increase in salivary flux or mucosal lesions.

The selected medicated tablets were evaluated for adhesion and erosion time and salivary concentration attained in healthy human volunteers.

Six volunteers (aged 22-32 years) participated in this study. The volunteers were instructed to finish their breakfast at least one hr prior to the study. Eating was restricted during the study while drinking was allowed *ad-libidum* from 60 min after administration of the muco-adhesive tablet. However no drinking was allowed 10 min before the collection of saliva.

The muco-adhesive tablets were applied by manually pressing them against the cheek for about 30 sec without moistening before application. The volunteers were instructed to record the time of tablet application and the time and circumstances of the end of adhesion (erosion or dislodgment).

Saliva samples (about 2 ml) were collected over 2 min period (1 min before and 1 min after the given time) and centrifuged at 1500 rpm for 4 min. 1 ml of the sample supernatant was taken, properly diluted and analyzed spectrophotometrically as for in vitro samples.

RESULTS AND DISCUSSION

Preformulation studies

The interaction of NTM with different polymers was examined by IR spectroscopy and differential scanning calorimetric (DSC) measurements. Fig. 2 shows IR spectra of NTM with different polymers. As shown in the figure, NTM has a carbonyl band of 1712 cm^{-1}. In the IR spectrum of the physical mixture for each polymer, no changes were observed in the NTM carbonyl band, which indicates that there are no interactions between NTM and any of the polymers.

More evidence of absence of an interaction is observed from the DSC thermograms (Fig. 3) where the thermogram of NTM was not changed by the presence of any of the bio-adhesive polymers used.

All the tablets were acceptable in regard to NTM content, weight variation and friability. Tablets with the highest hardness were obtained with carbopol 934p while tablets containing guar gum or NaCMC showed the lowest hardness. The differences in the tablet hardness were reported not to affect the release of the drug from hydrophilic matrices because the drug is released by diffusion through the gel layer and/or erosion of this layer and are therefore independent of the dry state of the tablet.[18]

In vitro drug release studies

The in vitro drug release from tablets prepared using different bio-adhesive polymers is shown in Figs. 4-8.

The release of NTM from bucco-adhesive tablets varied according to the type and ratio of the matrix-forming polymer.

The release rate of NTM decreased with increasing concentration of carbopol 934p. The drug release from carbopol 934p matrices may be attributed to that in the dry state, the drug is entrapped in the core of carbopol matrix. On hydration of the surface, a gelatinous layer is formed that consists of discrete microgels made up of many polymer particles in which the drug is dispersed. When the hydrogel is fully hydrated, it does not dissolve, but osmotic pressure from within works to break up the structure, mainly by sloughing off discrete pieces of the hydrogel. The hydrogels remain intact, and the drug continuously diffuses

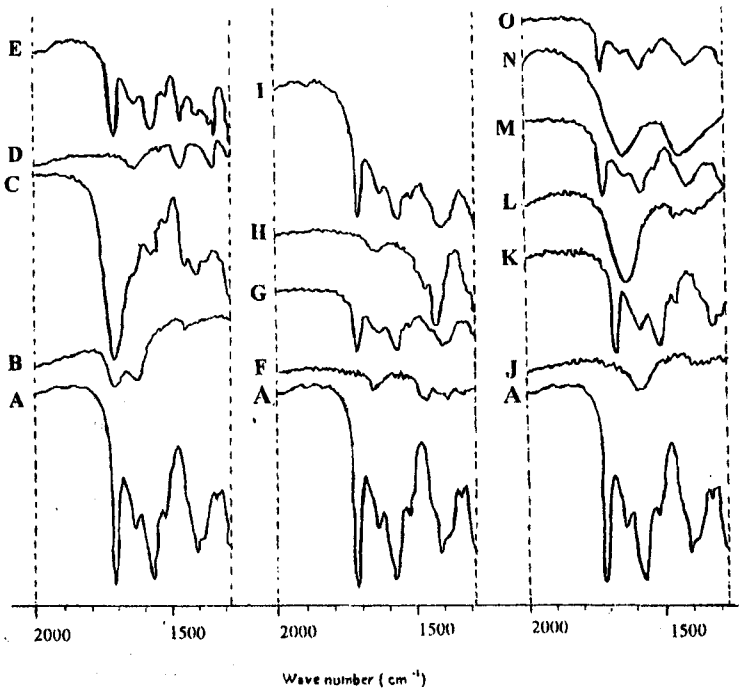

Fig. 2: IR Spectra of A: Natamycin alone, B: Carbopol 934p alone, C: Natamycin + Carbopol 934p, D: Polyethylene glycol 6000 alone, E: Natamycin + Polyethylene glycol 6000, F: Hydroxypropyl methyl cellulose alone, G: Natamycin + Hydroxypropyl methyl cellulose, H: Mannitol alone, I: Natamycin + Mannitol, J: Guar gum alone, K: Natamycin + Guar gum, L: Sodium alginate alone, M: Natamycin + Sodium alginate, N: Sodium carboxy methyl cellulose alone, O: Natamycin + Sodium carboxy methyl cellulose.

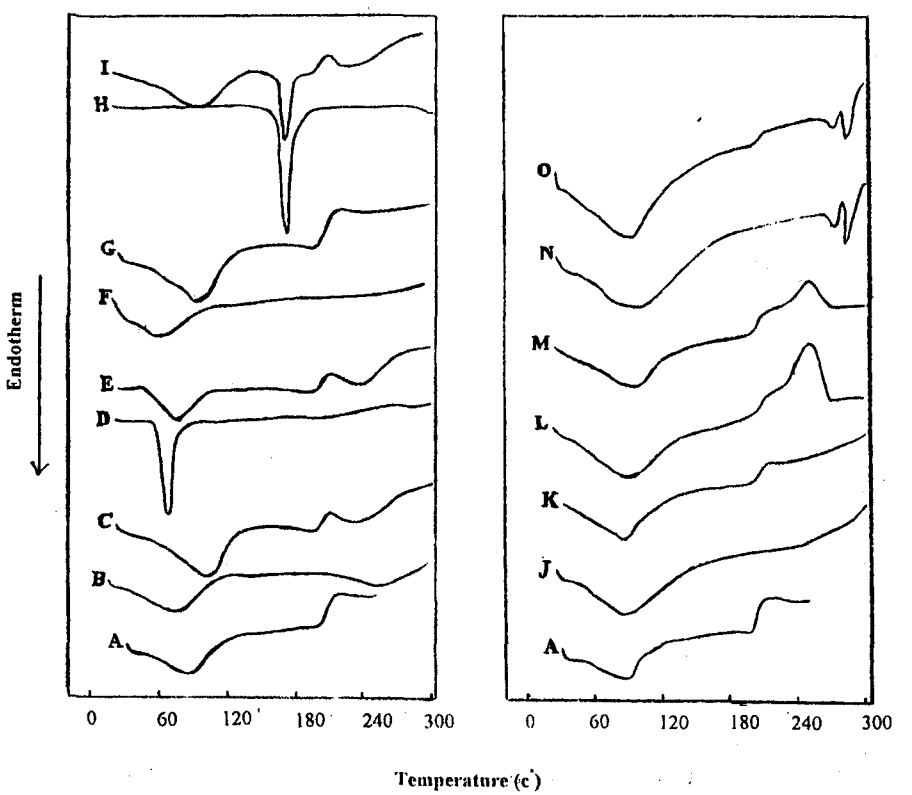

Fig. 3: DSC Profiles of A: Natamycin alone, B: Carbopol 934p alone, C: Natamycin + Carbopol 934p, D: Polyethylene glycol 6000 alone, E: Natamycin + Polyethylene glycol 6000, F: Hydroxypropyl methyl cellulose alone, G: Natamycin + Hydroxypropyl methyl cellulose, H: Mannitol alone , I: Natamycin + Mannitol, J: Guar gum alone, K: Natamycin + Guar gum, L: Sodium alginate alone, M: Natamycin + Sodium alginate, N: Sodium carboxy methyl cellulose alone, O: Natamycin + Sodium carboxy methyl cellulose.

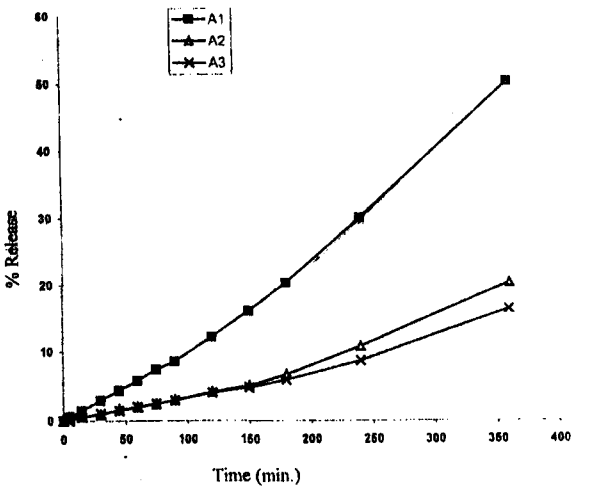

Fig. 4: In vitro release profiles of natamycin from bucco-adhesive tablet formulations containing different concentrations of carbopol 934p.

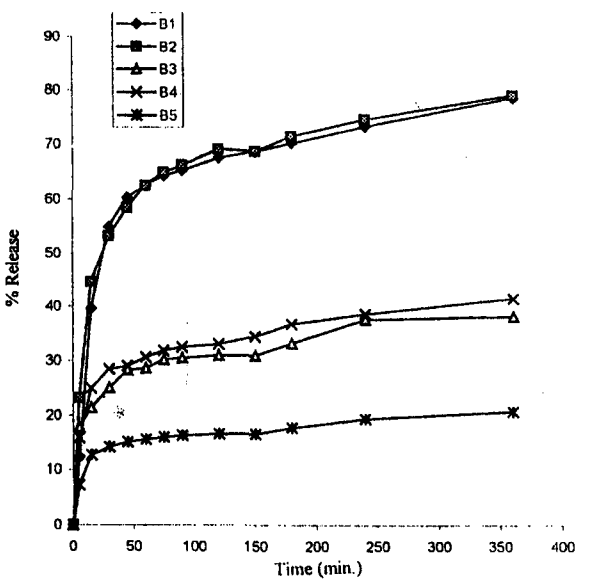

Fig. 5: In vitro release profiles of natamycin from bucco-adhesive tablet formulations containing different concentrations of guar gum.

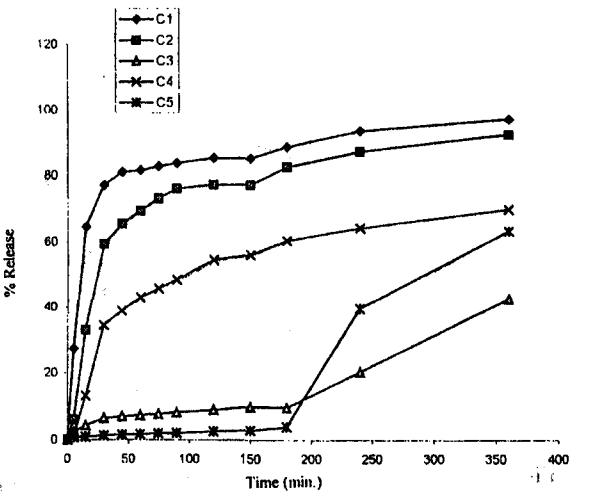

Fig. 6: In vitro release profiles of natamycin from bucco-adhesive tablet formulations containing different concentrations of Na CMC.

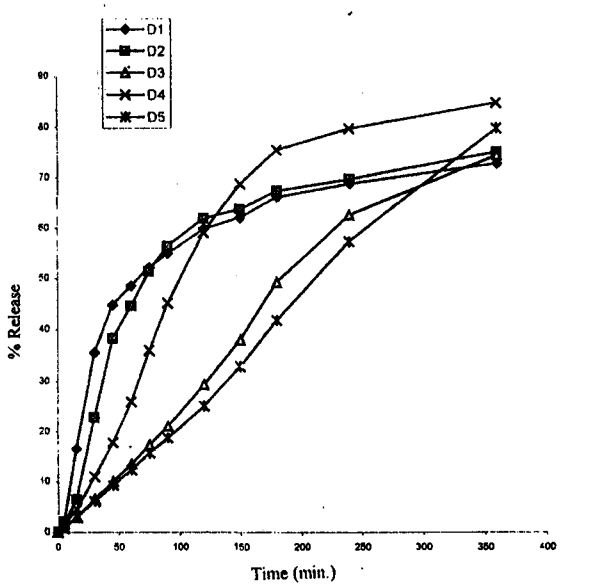

Fig. 7: In vitro release profiles of natamycin from bucco-adhesive tablet formulations containing different concentrations of HPMC.

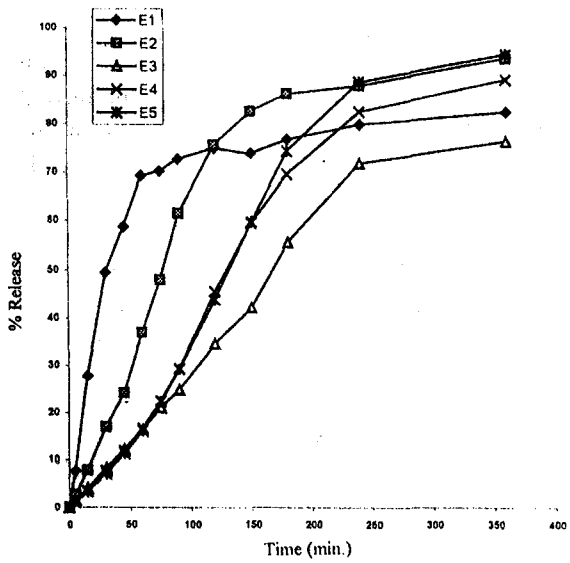

Fig. 8: In vitro release profiles of natamycin from bucco-adhesive tablet formulations containing different concentrations of sodium alginate.

through the gel layer at a more or less constant rate. It is postulated that as the concentration of the drug becomes high within the gel matrix and its thermodynamic potential increases, the gel layer around the tablet core act as a rate-controlling membrane, resulting in a linear release of the drug[19]

At lower concentrations e.g. at concentration levels 1 and 2 of formulations B, C, D and E, the bio-adhesive polymers did not seem to play a major role in determining the release pattern. At higher concentration of polymers, the release of the drug was found to be dependent on the type of the polymer as well as the total composition of the tablet. After 180 min, formulation C5 was laminated so the surface area from which the drug is released was increased and this explains the dramatic increase in the percent released of drug after 180 min. The mechanism of drug release seems to be tablet erosion as observed visually during the release study. However, at higher concentrations of polymer, the formulations containing guar gum exhibited swelling which was predominant over erosion. Formulation B5 formed a swollen matrix, which did not erode in 6 hr. The maximum drug concentration achieved in the dissolution medium using this formulation was much less as compared with other formulations. The polymers did not interfere with the analytical procedure.

To characterize the release mechanism of NTM, the dissolution data ($M_t / M_\infty < 0.60$) can be fitted to the exponential release equation.[20]

$$M_t / M_\infty = Kt^n \qquad (1)$$

Where M_t / M_∞ is the fraction of drug released up to time t, n is a diffusional exponent characterized the type of release mechanism operative during the dissolution process, K is a constant which incorporates the properties of the macromolecular polymeric system and the drug. The results of this fitting are presented in Table 3.

Table 3: Kinetic consatant (k), Diffusional Exponent (n) and correlation Coefficient (r^2) following linear Regression of Log (M_t/M_∞) versus Log (t) of bucco-adhesive tablets.

Batch no.	n	k	r^2
A1	1.077	0.74×10^{-4}	0.997
A2	1.049	0.32×10^{-4}	0.959
A3	1.323	0.073×10^{-4}	0.975
B1	0.864	0.032	0.982
B2	0.423	0.124	0.976
B3	0.177	0.135	0.987
B4	0.199	0.131	0.968
B5	0.210	0.062	0.941
C1	0.787	0.076	0.851
C2	1.315	0.726×10^{-3}	0.989
C3	0.547	0.8313×10^{-3}	0.912
C4	1.092	0.4×10^{-3}	0.916
C5	0.732	0.11×10^{-3}	0.778
D1	1.001	0.743×10^{-3}	0.944
D2	1.225	0.282×10^{-3}	0.989
D3	1.126	0.135×10^{-3}	0.999
D4	1.189	0.2×10^{-3}	0.998
D5	1.077	0.151×10^{-3}	0.999
E1	0.954	0.017	0.988
E2	1.058	0.46×10^{-3}	0.998
E3	0.995	0.285×10^{-3}	0.998
E4	1.187	0.139×10^{-3}	0.997
E5	1.133	0.171×10^{-3}	0.993

The value for n are nearly 1.0 for formulations containing carbopol 934p indicating a nearly zero-order kinetics of drug release (case II transport).

For the other formulations, the n value increased from 0.177 to 1.315 as the amount of water-soluble additives (PEG 6000 and mannitol) increased. This may be attributed to the fact that as the matrix swelled, the soluble additives was also removed by dissolution, thus decreasing the resistance of the gel layer to diffusion of drug. This resulted in shift of the release mechanism during dissolution process from non-fickian diffusion ($0.5 < n < 1$) to super case II transport ($n > 1$).

In vitro bio-adhesive strength

The muco-adhesive properties of formulations containing the same polymer were found to be a function of the concentration of the polymer (Table 4). The results are in agreement with an earlier study.[8] However, in formulations containing guar gum, NaCMC, HPMC or sodium alginate, it was found that the bio-adhesive strengths of formulations B4, C4, D4 and E4 decreased relative to B3, C3, D3 and E3 formulations inspite of containing the same amount of bio-adhesive polymer. This may be attributed to the higher mannitol content in formulations B3, C3, D3 and E3. This finding is in agreement with an earlier study reported by J. Ali *et al.*[21] The greater bio-adhesion exhibited by a system containing higher mannitol could be related to its spatial conformation and linear configuration which facilitated interaction between the adhesion sites (-OH groups) and the mucous layer. Among the formulations containing different polymers, those containing carbopol 934p exhibited maximum bio-adhesive strength followed by those containing NaCMC, HPMC, sodium alginate and guar gum.

Surface pH

The surface pH of formulations containing carbopol 934p was slightly acidic (5±0.26). The surface pH of other formulations was (6.48±0.39), so the surface pH of all the formulation was within satisfactory limits and hence these formulations should not cause any irritation in the buccal cavity.

Swelling index studies

The tablets were immersed in 50 ml phosphate buffer solution pH 6.8 maintained at 37°. The normalized swelling values of the tablets are in the order B > C ≥ E > A > D (Table 4). Formulations containing guar gum showed faster swelling compared to other formulations. In general, it was observed that the normalized swelling values increased with increasing the concentration of bio-adhesive polymer.

In vivo performance of placebo tablets

The bucco-adhesive tablets had an acceptable taste and were readily retained on the buccal mucosa. All the tablets eroded completely and none dislodged before complete erosion. No signs of local irritation were observed in any subject and no troubles at all were indicated. The mean residence time of the tablets was (97.47±60.81) min (Table 5).

In vivo evaluation of selected medicated bucco-adhesive tablets

Formula A3 was selected for further in vivo studies because it showed good in vivo adhesion time, no irritations and satisfactory in vitro drug release.

Figure (9) shows the mean salivary drug levels obtained with the selected tablets in healthy human volunteers. Table (6) lists the important parameters determined for the

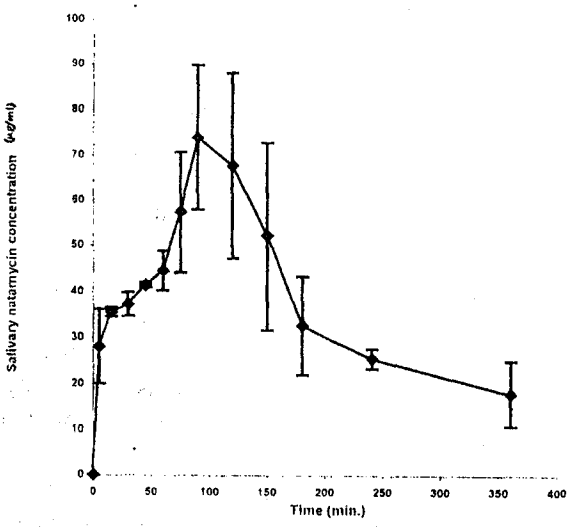

Fig. 9: Drug levels in saliva obtained with bucco-adhesive tablet formulations (n= 6) (values are expressed as mean ± SD).

Table 4: Important characteristics of different bucco-adhesive tablets, in vitro.

Formula	Bioadhesive strength (± SD) (g)	Surface PH (± SD)	Normalized swelling value (w_2/w_1) ± SD
A1	20.419±0.758	5.3±0.037	1.937±0.121
A2	40.192±0.991	4.9±0.09	2.254±0.025
A3	57.92±1.59	4.8±0.031	2.464±0.027
B1	7.492±0.57	6.470±0.062	Disintegrated
B2	13.997±0.67	6.03±0.12	6.712±0.190
B3	22.355±3.76	5.8±0.02	15.091±0.32
B4	12.549±1.55	5.85±0.05	7.5864±0.07
B5	23.73±0.56	6.22±0.055	13.8486±0.14
C1	12.276±0.94	6.13±0.057	Disintegrated
C2	25.891±0.549	6.18±0.08	Disintegrated
C3	34.523±0.61	6.36±0.052	4.658±0.193
C4	26.34±0.586	6.9±0.10	Disintegrated
C5	51.49±0.741	7.26±0.058	4.88±0.072
D1	9.762±0.506	6.4±0.01	Disintegrated
D2	13.077±1.519	6.6±0.032	Disintegrated
D3	26.542±1.809	6.78±0.076	1.119±0.16
D4	21.686±1.84	6.87±0.025	1.342±0.126
D5	32.86±0.27	7.14±0.04	1.534±0.04
E1	7.99±0.731	6.28±0.015	Disintegrated
E2	10.903±1.63	6.59±0.036	1.7417±0.139
E3	39.66±0.58	6.65±0.051	2.466±0.025
E4	28.79±1.12	6.69±0.025	2.964±0.247
E5	24.5±0.72	6.40±0.026	3.379±0.092

Values are mean of three readings ± SD.

Table 5: In-vivo evaluation of selected placebo bucco-adhesive tablets.

Formula	Time of adhesion[a]	Erosion/dislodgement	Irritation yes/no
A2	139.67±2.52	Erosion	No
A3	181.34±4.16	Erosion	No
B2	28±2.64	Erosion	No
B3	60.34±1.53	Erosion	No
C2	60±3	Erosion	No
C3	158.34±4.72	Erosion	No
D2	24.34±2.08	Erosion	No
D3	64.34±3.05	Erosion	No
E2	28.67±2.08	Erosion	No
E3	73.67±2.52	Erosion	No

[a] Mean of six values ± SD

Table 6: Certain important parameters of selected medicated bucco-adhesive tablets.
[n=6 , values are mean ± SD]

Formulation	Adhesion/Erosion time (min)	C_{max} (μg/ml)	T_{max} (min)	$T^{>MIC}$ (min)	AUC_{t0-tn} (μg min ml^{-1})
A3	150 (50.199)	73.878 (15.935)	93.75 (18.874)	320 (69.282)	13478.36 (3069.17)

formulation, in vivo. The results of the study revealed that the bucco-adhesive tablets were able to maintain the concentration of NTM in the saliva above the minimal inhibitory concentration (MIC) against *Candida albicans* (5 μg/ml)[22] for up to 6 hr.

The maintenance of salivary concentration of the drug even after complete erosion of the formulation could be attributed to reversible binding of the drug to the buccal mucosa.[23] The AUC_{t0-tn} and T > MIC values for the bucco-adhesive tablets were found to be (13478.36 ± 3069.17) μg.min.ml^{-1} and (320 ± 69.282) min respectively.

The results obtained from this study revealed that formulating it as bucco-adhesive tablets due to prolonged and controlled drug release could enhance the antifungal activity of NTM.

Conclusion

Buccal formulation of NTM in the form of muco-adhesive tablets were developed to a satisfactory level in terms of drug release, bio-adhesive performance and surface PH using different bio-adhesive polymers.

Although significant concentration of NTM could be achieved in the dissolution medium, the time of adhesion of some formulations was less than what would be expected. However, the results obtained from these formulations would be helpful for the further development of muco-adhesive buccal tablets. In vivo evaluation of the selected formulations showed that the tested polymers have low irritation potential and hence could be used for the development of buccal formulations. Therefore, we hope that in the near future these dosage forms will be a reality for use and become an alternative to controlled release dosage forms for the treatment of topical diseases.

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