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COMMUNICATIONS

Buccoadhesive Tablets Of Nifedipine : Standardization Of A Novel Buccoadhesive - Erodible Carrier.

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ABSTRACT

Buccoadhesive tablets of nifedipine were obtained by incorporation of nifedipine in suitable carrier systems standardised based on bioadhesion and dissolution. The carrier systems were formulated using sodium alginate as the bioadhesive. Mannitol, lactose, polyethylene glycol 6000 and polyethylene glycol 4000 were incorporated as solubilisers, singly or in combination. Carrier systems having a diameter of 11 mm and weighing about 200 mg were obtained by standard tabletting techniques using polyvinylpyrolidone as the binder. The systems were evaluated for bioadhesion and dissolution, 'in vitro' and 'in vivo' in seven normal healthy human volunteers. Based on these studies, nifedipine (5 mg) was incorporated in selected carrier systems to obtain buccoadhesive tablets of nifedipine. These tablets exhibited rapid 'in vitro' drug release.

INTRODUCTION

Nifedipine is a calcium antagonist found safe and effective for the treatment of moderate to severe hypertension[1]. Sublingual capsules of nifedipine are widely accepted in clinical practice for the treatment of hypertensive emergencies[2]. However, a number of drawbacks are associated with the sublingual capsule[3]. Hence administration via the buccal mucosa was considered.

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The buccal mucosa has an expanse of smooth and relatively immobile surface for placement of dosage forms. The introduction of the concept of bioadhesion in drug delivery now permits precise localisation of dosage forms on the mucosal surface[4]. Mucoadhesive systems have generally been investigated as platforms for controlled drug delivery[5-7]. The present study however reports a novel mucoadhesive rapid release carrier system which could be localised on the buccal mucosa. This new buccoadhesive system would erode to release drug at a rate facilitating rapid absorption through the oral mucosa.

Buccoadhesive systems were formulated using a combination of bioadhesive polymer and solubilizers. Sodium alginate was selected as the bioadhesive[8] polymer. Mannitol, lactose, polyethylene glycol 4000 and polyethylene glycol 6000 were the solubilisers investigated. The study was carried out in two parts. The first part of the study dealt with standardisation of the buccoadhesive carrier system. This part of the study was designed to ensure the feasibility of developing a buccoadhesive carrier which would be adequately retained on the buccal mucosa even as it eroded in about 30 min in the oral cavity. The second part of the study deals with the 'in vitro' evaluation of buccoadhesive tablets of nifedipine obtained by incorporation of nifedipine in selected carrier systems.

EXPERIMENTAL

Materials : Nifedipine, USP was obtained as a gift from Unichem Laboratories Ltd., India. Sodium alginate was procured from Loba Chemie, India. Polyvinylpyrolidone (PVP molecular weight 44,000) and mannitol were acquired from BDH Chemicals, U.K., polyethylene glycols (PEG 4000 and PEG 6000) were obtained as a gift from Hico Products, India. Lactose was of B.P. standard. All other chemicals used were of pharmaceutical grade.

Preparation of the Buccoadhesive carrier systems : The carrier systems were prepared by conventional wet granulation technique using a hydroalcoholic binder. The bioadhesive was combined with the solubilisers mannitol, lactose, PEG 4000 and PEG 6000 either singly or in combination as listed in table 1. Polyvinylpyrolidone (15% w/w) was included in all the formulations as a dry binder. Granules were compressed on a single stroke tablet press equipped with flat punches (diameter 11 mm, Cadmach India Ltd.) to obtain tablets weighing around 200 mg.

Nifedipine when incorporated, was included either as a fine powder (-200 #) or as a solid dispersion in

TABLE 1

Composition of Buccoadhesive Carrier Systems.

Formulation Code	Conc. of bioadhesive	Conc. of solubilizer		
	Sod. alginate %W/W	Mannitol %W/W	PEG6000 %W/W	PEG4000 %W/W
M1	5	80	-	-
M2	10	75	-	-
M3	15	70	-	-
M4	20	65	-	-
M5	25	60	-	-
M6	50	35	-	-
M7	85	-	-	-
M8	5	35	45	-
M9	10	35	40	-
M10	15	35	35	-
M11	20	35	30	-
M12	25	35	25	-
M13	50	-	35	-
M14	5	35	-	45
M15	10	35	-	40
M16	15	35	-	35
M17	20	35	-	30
M18	25	35	-	25
M19	50	-	-	35

Similar compositions containing lactose instead of mannitol were formulated and were labelled as L1,L2,L3....,L19.

PEG 6000 (1:10). The drug was blended with the excipients prior to granulation.

Evaluation of the carrier systems :

'In vitro' evaluation : Bioadhesion :

Bioadhesion was determined following a reported method*. The instrument employed to evaluate bioadhesion was the Universal tensile apparatus "Instron" (model 1126, Instron Ltd., U.K.). The instrument provided for recording the maximum force at detachment. A

load range of 0-100 gm was deployed on the Y-axis. The cross head speed was kept at 200 mm/min and chart to cross head drive speed at 1:1. Special test cells (adaptors) were designed to hold the biological tissue. The biological tissue used was guinea pig ileal mucosa obtained immediately after sacrifice of the animal. Fresh tissue was used for each sample. The test medium com prised of 0.2 ml phosphate buffer pH 6.2 and a contact time of 2 minutes was allowed. The maximum force at detachment was recorded on a minimum of three samples for each composition studied.

'In vitro' Evaluation : Dissolution :

The time required for complete dissolution of the carrier system was determined using a disintegration test apparatus (USP XXI). The dissolution of six tablets of each formulation was studied at 37°C in distilled water.

'In Vivo' Evaluation :

Seven healthy human volunteers in the age group 21 to 25 years participated in this study. A carrier system was placed on the buccal mucosa between the cheek and gingiva of each volunteer. The volunteers were asked to monitor the ease with which the system was retained on the mucosa and note any tendency for detachment. The time taken for the tablet to dissolve completely was simultaneously monitored by carefully observing for residual polymer on the mucosa. In addition, volunteers were asked to comment on the acceptability of these formulations.

Buccoadhesive tablets of nifedipine : The tablets were evaluated for bioadhesion, dissolution and 'in vitro' drug release. The drug content of the tablets of each formulation was analysed before the 'in vitro' dissolution rate test in six tablets. The kinetics of nifedipine released was determined in six tablets of each formulation in the USP dissolution rate test apparatus I at 100 r.p.m. A volume of 100 ml methanol and water (3:7) was used as dissolution medium. The drug released was determined by ultraviolet spectrophotometry at 238 nm (Beckman DB Spectrophotometer).

RESULTS AND DISCUSSION

Evaluation Of Buccoadhesive Carrier Systems :

Bioadhesion :'In vitro' evaluation :

The bioadhesive force recorded is graphically represented in figures 1(a) and (b). It can be appreciated from the figures that an increase in bioadhesive concentration upto 20% led to an increase in bioadhe-

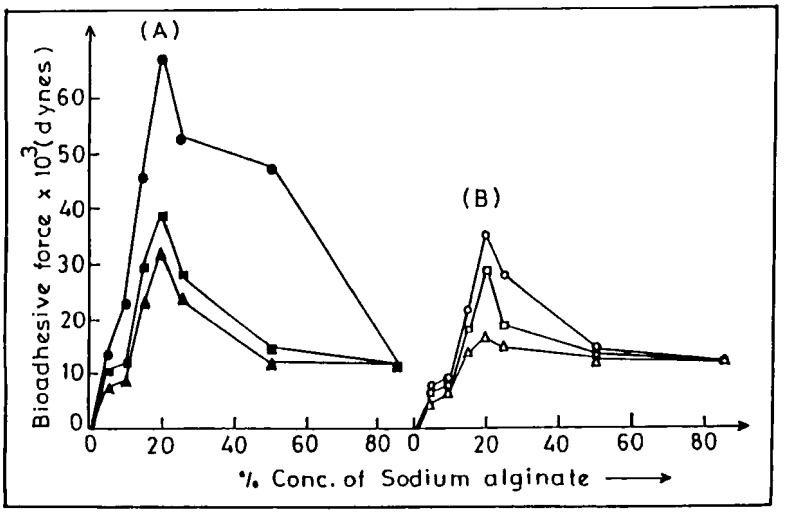

FIGURE 1 : Bioadhesive Force Of Buccoadhesive Carrier Systems.

sion. Further increase resulted in a reduction in the recorded bioadhesive force. This pattern was exhibited irrespective of the nature of the solubilizer and is explained as suggested by Robinson et al[10]. Increase in bioadhesive concentration beyond 20% resulted in weakening of the polymer-polymer interactive forces due to increased hydration of the systems. This caused rupture of the systems prior to detachment from the mucosal surface. It is also evident from the same figures that formulations containing mannitol as solubilizer exhibited greater bioadhesion than formulations containing the same proportions of lactose. Likewise formulations of mannitol in combination with polyethylene glycol were more bioadhesive than corresponding formulations of lactose in combination with polyethylene glycol. The greater bioadhesion exhibited by systems containing mannitol could be related to its spatial conformation and linear configuration which facilitated interaction between the adhesive sites (-OH groups) and the mucus layer[8]. Systems containing polyethylene glycol revealed minimum bioadhesion corroborating the finding[8] that polyethylene glycols are poor bioadhesives. The lower bioadhesive force exhibited by systems containing PEG 4000 in comparison with those containing PEG 6000 is attributed to its lower molecular weight, as it has been reported[8] that bioadhesive force decreases with decrease in molecular weight.

Bioadhesion :'In vivo' evaluation :

The 'in vitro' bioadhesive force decreased when the bioadhesive concentration exceeded 20%, however, systems with 20% or more of sodium alginate were adequately retained on the buccal mucosa 'in vivo'. Moreover, movement of the jaw simulating talking or gulping did not dislodge the systems. Systems with 85% sodium alginate were reported to be extremely sticky and unacceptable while those with less than 20% sodium alginate were dislodged even before they dissolved completely.

Dissolution :'In vitro' evaluation :

An increase in bioadhesive concentration led to increased dissolution time, while an increase in the solubiliser concentration resulted in faster dissolution as seen from figure 2. The nature of the solubiliser did not elicit a pronounced effect on dissolution time. However systems con taining 25% w/w of bioadhesive or lower (except for systems of lactose in combination with PEG 6000) revealed desirable dissolution characteristics (dissolved completely in less than 35 minutes). It could therefore be surmised that the bioadhesive concentration played a major role in controlling dissolution of the systems.

Dissolution : 'In vivo' evaluation :

A good correlation between 'in vitro' and 'in vivo' dissolution time is observed from table 2. The systems gradually eroded without causing excessive salivation, an indication that loss of drug perorally would be minimal. These buccoadhesive carrier systems would therefore ensure maximal drug absorption through the oral mucosa and were considered for drug incorporation.

Systems M4 and M11 revealed maximum 'in vitro' bioadhesive force. 'In vivo', they exhibited the desired buccoadhesive and dissolution characteristics. Hence drug was incorporated in these systems to obtain buccoadhesive tablet formulations of nifedipine containing 5mg of the drug. (Table 3)

Evaluation of buccoadhesive tablets of nifedipine :

Formulation A revealed greater bioadhesive force than formulation B which contained PEG 6000. The bioadhesive force recorded for both the formulations was not markedly different from those of the respective carrier systems (Table 3) and the time taken for complete dissolution of both the formulations was less than 30 minutes despite incorporation of the hydrophobic drug nifedipine.

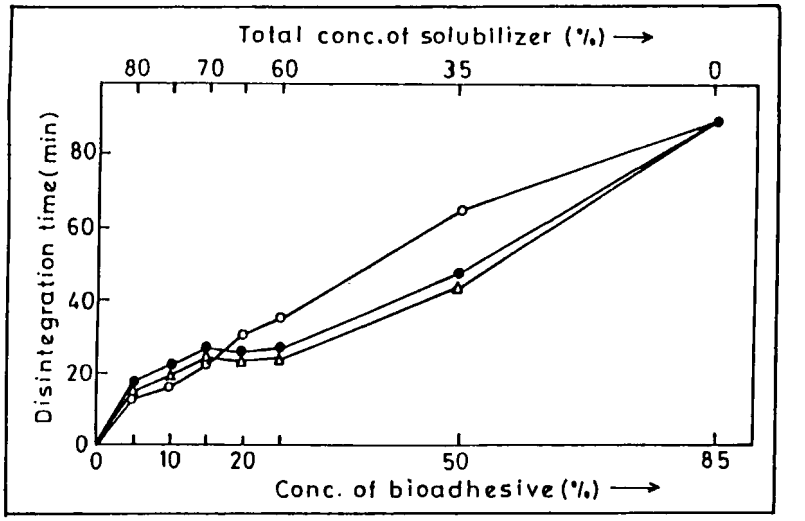

FIGURE 2 : "In-Vitro" Dissolution Time Of Buccoadhesive Carrier Systems.

TABLE 2

'In vitro' and 'In vivo' dissolution time for buccoadhesive carrier systems.

Composition Code	Dissolution time In vitro (min)	In vivo (min)
M1	13	10 - 15
M2	16	15 - 20
M3	23	20 - 25
M4	31	30 - 35
M5	35	35 - 40
M6	65	60 - 65
M7	90	90 - 100
M11	25	20 - 25
M17	26	25 - 30
L11	40	30 - 40
L17	30	30 - 40

TABLE 3
"In vitro" evaluation of buccoadhesive tablets of nifedipine

Formulation code	A	B
Composition		
Bioadhesive	20% w/w Sod. alg.	20% Sod. alg.
Solubiliser	62.5% Mannitol	35.5% Mannitol + 25% PEG 6000
Bioadhesive force (Dynes)	63.88×10^3 (67.62×10^3)	35.86×10^3 (39.69×10^3)
Dissolution time	22.00 min	24.00 min
$T_{50\%}$	6.55 min	3.46 min
$T_{90\%}$	18.97 min	9.47 min

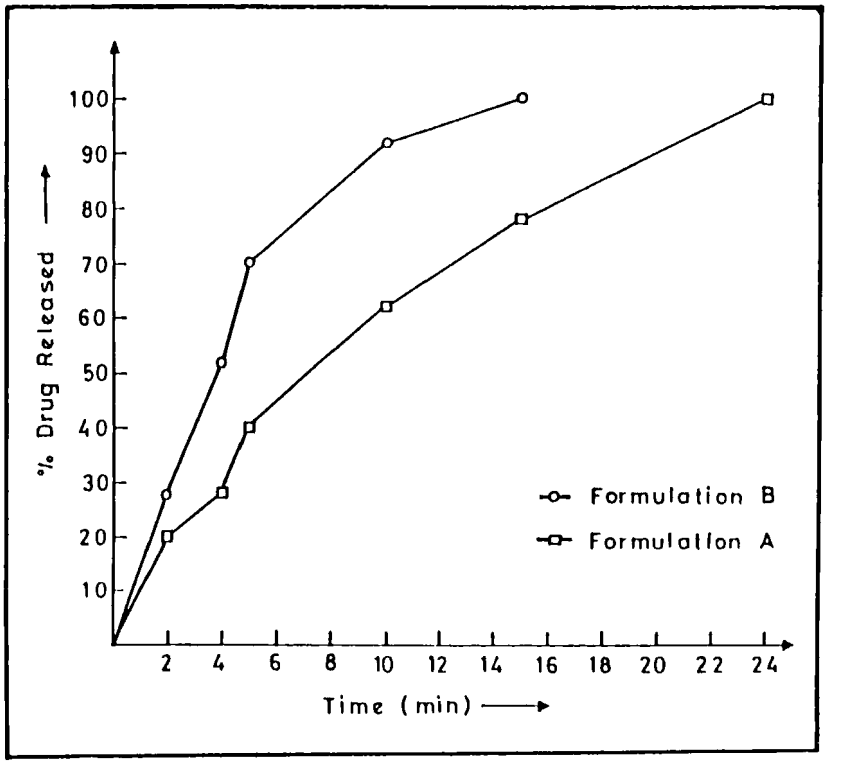

FIGURE 3 : Drug Release Profiles Of Buccoadhesive Tablets Of Nifedipine.

'In vitro' drug release : Formulation B revealed faster 'in vitro' drug release than formulation A (Figure 3). The $T_{80\%}$ and $T_{90\%}$ values are represented in table 3. The faster 'in vitro' drug release from formulation B could be attributed to the inclusion of drug as a solid dispersion in PEG 6000[11].

CONCLUSION

It can be concluded from the present study that buccoadhesive erodible carriers represent a novel system for drug administration via the oral mucosa. The application of the buccoadhesive tablet formulation B which exhibited rapid 'in vitro' drug release haas been demonstrated for the treatment of hypertensive emergencies[10].

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