J. Pharm. Pharmacol. 1994, 46: 192–195
Received February 18, 1993

Comparative Study of Buccoadhesive Formulations and Sublingual Capsules of Nifedipine

TANUJA SAVE, MEENA U. SHAH*, A. R. GHAMANDE† AND PADMA VENKITACHALAM

*Pharmaceutical Division, Department of Chemical Technology, Bombay University, Matunga, Bombay 400 019, *Bhatia Medical Research Centre, Bombay and †St George's Hospital, Bombay, India*

Abstract—The pharmacodynamics of nifedipine administered via the oral mucosa was investigated in hypertensive patients. The effect of two buccoadhesive formulations, tablets and films, was compared with the commercially available sublingual capsule in a complete cross-over study in six patients. All three formulations elicited onset of action 10 min after administration. The sublingual capsule and the buccoadhesive film revealed peak response at 30 min. The buccoadhesive tablet, however, exhibited a delayed peak response at 45 min. Analysis of variance indicated that, although time-dependent differences in the formulations were suggested, there was no significant difference in the overall effect produced by the three formulations. The results of the study suggest that the buccoadhesive formulations of nifedipine were comparable in performance with the sublingual capsule.

Nifedipine is a calcium antagonist which selectively inhibits the transmembrane influx of calcium ions into vascular smooth muscle cells (Sorkin et al 1985). As the contractile process depends on the movement of extracellular calcium into the cells, administration of nifedipine results in the dilatation of the vascular bed (Lehman et al 1983). Peripheral resistance is thus reduced and blood pressure is lowered (Robinson et al 1980).

The difficulties presented in the administration of drugs for the treatment of hypertensive emergencies are largely overcome by the use of nifedipine sublingually (Masotti et al 1985). Sublingual administration has been found safe and effective in the treatment of moderate to severe hypertension (Erbel et al 1983) and is used in clinical practice. However, this mode of administration has a number of limitations. Sublingual administration of nifedipine involves cutting open the soft gelatin capsule and pouring the contents beneath the tongue. The patient is then required to retain the contents in the mouth for a minimum of 10 min. This mode of administration results in dosage inaccuracy as the capsule shell invariably retains part of the drug. The contents of the capsule are bitter and fluid in nature, and therefore difficult to retain in the mouth. Hence buccoadhesive tablets and films which could be conveniently administered and could provide an accurate dose of the drug while being easily retained in the mouth have been formulated. The specific objective of this study was to evaluate the pharmacodynamics of the buccoadhesive formulations in comparison with the clinically accepted sublingual soft gelatin capsule (Depin, Cadila Laboratories Ltd, India) containing 5 mg of the drug.

Reduction in blood pressure is a direct reflection of the efficacy of antihypertensive drugs and their formulations (Rudd & Blaschke 1985). The formulations were therefore evaluated for their in-vivo performance by monitoring the reduction in systolic and diastolic blood pressure in six hypertensive patients in a complete cross-over study.

Correspondence: P. Venkitachalam, Pharmaceutical Division, Department of Chemical Technology, Bombay University, Matunga, Bombay 400 019, India.

Materials and Methods

Materials

Nifedipine was obtained as a gift from Unichem Labs Ltd, India. All the other ingredients were of pharmaceutical grade.

Buccal tablets contained 5 mg nifedipine and comprised 20% w/w sodium alginate as bioadhesive polymer, 15% w/w polyvinylpyrolidone, 37·5% w/w mannitol, 25% w/w polyethylene glycol (PEG) 6000 and 2·5% w/w nifedipine. A solid dispersion of nifedipine in PEG 6000 (1 : 10) was seen to exhibit rapid in-vitro dissolution (Save & Venkitachalam 1992). Nifedipine was therefore incorporated as a solid dispersion in PEG 6000. Buccal films were cast from an aqueous gel containing 1·5% w/v sodium alginate and 1% w/v methyl cellulose as bioadhesives, 0·5% w/v polyvinylpyrolidone, 0·3% w/v mannitol, 0·3% w/v PEG 6000 and 1% v/v glycerol to obtain films containing 5 mg nifedipine per dosage form (4 cm^2). The properties of the buccoadhesive tabets and films, and their stability are recorded in Tables 1 and 2, respectively. The tensile strength of the films was measured on the Universal Tensile Tester, while the other properties were determined by the method of Baichwal (1985). Drug content of the formulations was measured spectrophotometrically at 238 nm on a Beckman DB spectrophotometer. The stability samples were analysed spectrophotometrically after ensuring the absence of degraded products by thin-layer chromatography. The in-vitro drug release studies were carried out in the USP Dissolution Apparatus I in 100 mL methanol and water (3 : 7) as the dissolution medium.

Patient selection

The selection of patients was carried out using the guidelines suggested by Stanley et al (1988) who conducted similar studies on antihypertensive formulations. Patients with essential hypertension graded mild to moderate were preferred for the trial (stable diastolic blood pressure between 95 and 115 mmHg at home (sitting) and in the outpatient clinic (supine)). Patients suffering from cardiac failure, heart block, myocardial ischaemia, impaired liver or kidney function,

diabetes mellitus requiring drug or insulin therapy, myocardial infarction or history of asthma were excluded from the trial. Hypertensive patients who had a diagnosis or history of hypersensitivity to nifedipine or a heart rate less than 50 beats min^{-1} were not chosen for the trial. Pregnant and breastfeeding women, paediatric and geriatric patients were also excluded. Patients in the age group 30–60 years were preferred. Lastly, co-operation of the patients was an important criteria for selection.

At the initial visit to the physician, patients were screened for entry and if found eligible, their written consent to participate in the trial was obtained. Their medical history and adverse experiences were recorded. Patients selected for the trial were subjected to a physical examination in addition to vital sign measurement. The measurement of vital signs comprised an assessment of blood pressure and heart rate. Blood pressure was measured using a standard sphygmomanometer. Sitting blood pressure was measured after at least 5 min rest and twice again at an interval of 1 min. The mean of the three readings was considered for evaluation. The heart rate was manually measured after the second blood pressure reading. Six patients, three males and three females averaging 41 ± 3 years of age, with uncomplicated mild to moderate essential hypertension were selected. Their body weight averaged 53 ± 5 kg, and height averaged 160 ± 5 cm. Average values for sitting blood pressure in the outpatient clinic were 149 ± 4 mmHg systolic, 106 ± 2 mmHg diastolic and 120 ± 3 mmHg mean blood pressure. Aside from essential hypertension no patient had any acute or chronic illness. The patients were nonsmokers and were known not to abuse alcohol or drugs. They were requested not to make any changes in their dietary, smoking and social habits during the period of study. Patients selected for the trial were instructed not to take any cardiovascular drugs from at least 24 h before testing.

Study protocol

A complete cross-over study was performed such that each patient received all three formulations in the order, sublingual capsule, buccal tablet and buccal film. A period of one week was allowed between administrations.

The tip of the soft gelatin capsule was cut open with a sterile scissor. The contents of the capsule were emptied as completely as possible into the sublingual cavity. The patients were advised to retain the contents in the mouth for a minimum of 10 min. Buccoadhesive tablets and films were placed between the gingiva and the cheek and were retained in position due to their bioadhesive nature. The patients were advised not to disturb the formulations.

Systolic and diastolic blood pressure were recorded at 5, 10, 15, 20, 30, 45, 60, 90, and 120 min post-administration following the procedure described earlier for vital sign measurement. Patients were continuously monitored for side-effects. At the end of the study, patients were asked to comment on the comparative acceptability of the formulations.

Statistical evaluation

Results are expressed as mean $\pm$ s.e.m. Data were analysed by analysis of variance.

Results and Discussion

In-vitro evaluation

The properties of the buccoadhesive formulations are shown in Tables 1 and 2. It is evident from the tables that both the

Table 1. Effect of accelerated storage conditions on the properties of buccoadhesive tablets at the end of two months.

Properties		Storage conditions				
	Initial values	Ambient	37°C	45°C	60°C	75% r.h.
Drug content % ($\pm$s.d.)	100·14 (1·14)	100·30 (1·98)	100·04 (2·40)	101·68 (2·06)	98·34 (1·91)	99·86 (2·83)
Hardness (kg cm^{-2})	4·00	4·00	4·00	2·50	1·50	3·50
Friability (%)	0·71	0·72	0·72	0·68	0·42	0·70
Weight gain/loss (% w/w)	—	—	—	−1·73	−6·34	0·01
Disintegration time (min)	24·00	21·50	22·50	25·00	28·00	21·50
*Time for 50% dissolution (min)	3·46	3·67	3·44	4·60	7·35	3·44
*Time for 90% dissolution (min)	9·47	9·41	9·56	11·65	16·20	9·59

Each value represents a mean of three readings, *each value represents a mean of six readings.

Table 2. Effect of accelerated storage conditions on the properties of buccoadhesive films at the end of two months.

Properties		Storage conditions				
	Initial values	Ambient	37°C	45°C	60°C	75% r.h.
Drug content % ($\pm$s.d.)	100·76 (0·68)	100·62 (1·67)	100·86 (0·62)	100·22 (1·81)	101·52 (1·87)	100·36 (1·87)
Tensile strength $\times 10^6$ (dynes cm^{-2})	136·21	138·02	142·68	148·21	172·76	134·02
Flatness (%)	100·00	100·00	100·00	94·00	90·00	100·00
Folding endurance	>1800	>1800	>1800	800	—	>1800
Weight gain/loss (% w/w)	—	—	—	−1·47	−6·34	—
*Time for 50% dissolution (min)	4·61	5·70	5·69	7·08	10·14	5·80
*Time for 90% dissolution (min)	16·37	16·68	16·81	19·84	26·04	16·66

Each value represents a mean of three readings, *each value represents a mean of six readings.

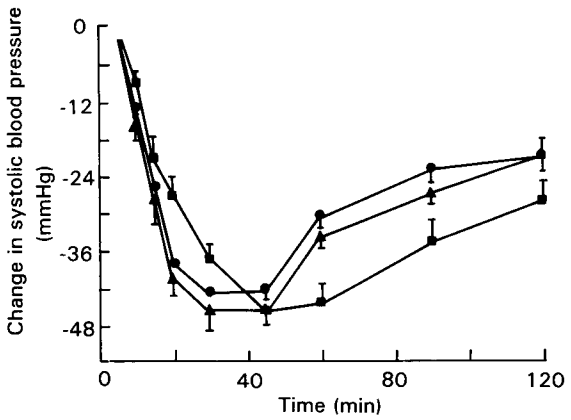

FIG. 1. Average reduction in systolic blood pressure after the administration of (●) sublingual capsule, (▲) buccal film and (■) buccal tablet. Values are expressed as means ± s.e.

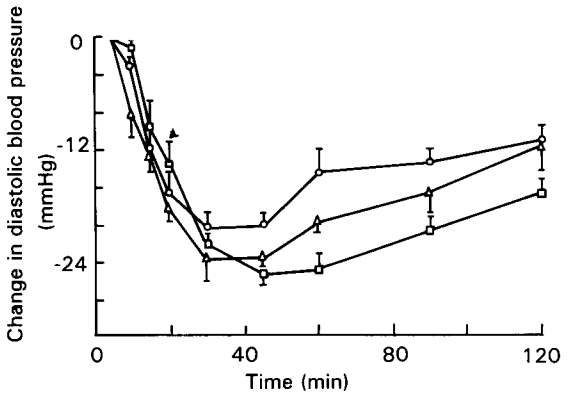

FIG. 2. Average reduction in diastolic blood pressure after the administration of (○) sublingual capsule, (△) buccal film and (□) buccal tablet. Values are expressed as means ± s.e.

formulations exhibited excellent drug content uniformity. No marked changes in properties were observed in the formulations exposed at ambient conditions, 37°C and 75% r.h. However, changes in properties were significant in formulations exposed at 45 and 60°C. These changes could be attributed either to the physical instability of PEG 6000, a low-melting excipient in the formulation or to the loss of moisture at these temperatures. No significant reduction in the content of active drug occurred over a period of two months. Hence, the shelf-life of the formulations could be extrapolated to a minimum of two years (Kennon 1964). Storage temperatures not exceeding 40°C and light-resistant strip packing are essential to ensure stability of these formulations.

Reduction in systolic blood pressure

The average reduction in systolic blood pressure produced by the three formulations is depicted in Fig. 1. All three formulations elicited onset of action 10 min after administration. The sublingual capsule and buccal film formulations revealed peak responses at 30 min. A similar finding has also been reported for the sublingual capsule (Sorkin et al 1985). The buccal tablet, however, elicited a delayed peak response at 45 min. Subsequently a gradual increase in blood pressure occurred.

Split-plot analysis of variance (Table 3) revealed that there was no significant difference between the overall averages of the three treatment groups ($P > 0.05$). However, the computed F value for time{T} × formulation{F} (a measure of interaction which compares the parallelism of the three curves) indicates a significant difference among the three formulations ($P < 0.05$). This revealed that although time-dependent differences in the formulations were suggested, there was no significant difference in the overall effect

Table 3. Repeated measures (split plot) analysis of variance for comparative decrease in systolic blood pressure after administration of the three formulations.

Source of variation	Degrees of freedom	Sum of squares	Mean squares	F value (computed)
Patients	15	2546·62	169·77	
Time (T)	8	29611·02	3701·38	$F_{(2,15)} = 0.29$
Formulation (F)	2	98·23	49·12	
T × F	16	2275·24	142·20	$T \times F_{(16,120)} = 4.22$*
Error (within treatments)	120	4042·19	33·68	
	161	38573·30	4096·15	

*$P < 0.05$.

Table 4. Repeated measures (split plot) analysis of variance for comparative decrease in diastolic blood pressure after administration of the three formulations.

Source of variation	Degrees of freedom	Sum of squares	Mean squares	F value (computed)
Patients	15	785·99	52·39	
Time (T)	8	8624·89	1078·11	$F_{(2,15)} = 2.05$
Formulation (F)	2	215·12	107·56	
T × F	16	736·80	46·05	$T \times F_{(16,120)} = 5.85$*
Error (within treatments)	120	945·30	7·88	
	161	11308·10	1291·99	

*$P < 0.05$.

produced by the three formulations. The response obtained at each time interval was also analysed by comparative one-way analysis of variance followed by least significant difference analysis. This analysis indicated that the effect produced by the sublingual capsule and buccal film revealed no significant time-dependent difference ($P<0.05$). The buccal tablet, however, revealed a significantly lower effect at 20 min and a greater effect at 60 min ($P<0.05$). The buccal film could, therefore, be considered comparable with the sublingual capsule, whereas the buccal tablet produced an equivalent response with a slightly delayed effect.

Reduction in diastolic blood pressure

As observed for systolic blood pressure, all three formulations elicited onset of action at 10 min. However, the initial response (10 min) produced by the buccal film was appreciably higher ($P<0.05$). Likewise, the sublingual capsule and buccal film revealed peak response at 30 min while the buccal tablet elicited a peak response at 45 min. A decline in response followed and a gradual rise in diastolic blood pressure occurred (Fig. 2).

Split-plot analysis of variance for diastolic pressure is reported in Table 4. The overall average response elicited by the three formulations was comparable ($P>0.05$). These observations were similar to that observed for changes in systolic blood pressure. A comparative one-way analysis of variance followed by least significant difference analysis illustrated the time-dependent differences between the formulations. The initial response produced by the buccal film was seen to be significantly higher than that produced by the other formulations ($P<0.05$). At 45 min, even as the response produced by the film was decreasing, the effect was significantly higher than the capsule ($P<0.05$). Beyond 45 min the response was seen to be comparable with that of the sublingual capsule and markedly lower than that produced by the tablet. The response produced by the buccal tablet was comparable with that of the capsule until peak response was attained at 45 min. Beyond 45 min the tablet produced a significantly greater reduction in diastolic pressure in comparison with the other two formulations. Both the buccoadhesive formulations, namely the film and the tablet, could thus be considered comparable in performance to the sublingual capsule.

It has been recently reported that administration through the buccal mucosa does not give the rapid onset of absorption as seen with sublingual delivery (Robinson & Harris 1992). The results of the present study, however, reveal that the buccal route of administration could be utilized for rapid onset of action through appropriate formulation design. The delay in peak response observed with the buccal tablet is attributable to its lower surface area and greater thickness (0·95 cm^2, 1·62 mm) in comparison with that of the buccal film (4 cm^2, 0·115 mm).

The buccoadhesive formulations had an acceptable sweet taste and were readily retained on the buccal mucosa. They dissolved gradually and left no papable residue in the mouth. Normal movement of the tongue and jaw did not dislocate the dosage forms whereas retaining the liquid contents of the sublingual capsule required cessation of normal jaw movement for a certain time period. The buccoadhesive formulations delivered a fixed dose of the drug, while the sublingual capsule delivered a maximum of 92% drug on emptying (estimated by spectrophotometric analysis of the extruded contents). In addition, patients reported a tendency to swallow the contents of the sublingual capsule.

The buccoadhesive formulations of nifedipine revealed a good potential for rapid reduction of blood pressure in hypertension. It can be appreciated from the data that while these formulations were comparable in response to the sublingual capsule, they were superior in patient acceptability and provided a fixed dose of the drug. It could thus be concluded that these formulations could successfully overcome the limitations of the sublingual capsule without compromising therapeutic efficacy.

References

Baichwal, M. R. (1985) Polymer films as drug delivery systems. In: Proceedings of the International Symposium on Advances in Drug Delivery Systems. M.S.R. Foundation, Bombay, pp 128–147

Erbel, R., Meyer, J., Brand, G., Effert, S. (1983) Emergency treatment of hypertensive crisis with sublingual nifedipine. Postgrad. Med. J. 59 (Suppl. 3): 134–136

Kennon, L. (1964) Use of models in determining chemical pharmaceutical stability. J. Pharm. Sci. 53: 815–818

Lehman, H. V., Hochrein, H., Witt, E., Mies, H. W. (1983) Haemodynamic effects of calcium antagonists: review. Hypertension 5: II 66–II 73

Masotti, G., Morettini, A., Galanti, G., Paoli, G., Poggesi, L. (1985) Antihypertensive action of nifedipine: effects on arteries and veins. J. Clin. Pharmacol. 25: 27–35

Robinson, B. F., Dobbs, R. J., Kelsey, C. R. (1980) Effects of nifedipine on resistance vessels, arteries and veins in man. Br. J. Clin. Pharmacol. 10: 433–438

Robinson, J. R., Harris, D. (1992) Drug delivery via the mucous membranes of the oral cavity. J. Pharm. Sci. 81: 1–10

Rudd, P., Blaschke, T. F. (1985) Cardiovascular drugs: antihypertensive agents and the drug therapy of hypertension. In: Gilman, A. G., Goodman, L. S., Rall, T. W., Murad, F. (eds) The Pharmacological Basis of Therapeutics. Macmillan, New York, pp 784–805

Save, T. K., Venkitachalam, P. (1992) Studies on solid dispersions of nifedipine. Drug Dev. Ind. Pharm. 18: 1663–1679

Sorkin, E. M., Clissold, S. P., Brogden, R. N. (1985) Nifedipine: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in ischemic heart disease, hypertension and related cardiovascular disorders. Drugs 30: 182–274

Stanley, N. N., Thirkettle, J. L., Varma, M. P. S., Larkin, H., Heath, I. D. (1988) Efficacy and tolerability of atenolol, nifedipine and their combination in the management of hypertension. Drugs 35 (Suppl. 4): 29–35