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Buccal delivery of Isradipine from mucoadhesive buccal tablets

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ABSTRACT

The present research work describes the improvement of bioavailability of Isradipine through buccal delivery. Isradipine buccal tablets were prepared with β cyclodextrin which improved the photostability of the drug. Buccal formulations were evaluated for in vitro release, moisture absorption, mechanical properties, and bioadhesion, and optimized formulation was subjected for bioavailability studies in healthy human volunteers and compared with marketed tablet. The pharmacokinetic parameters C_{max}, t_{max} and AUC_{o-t} of test formulation were calculated and compared with the reference i.e., marketed product. It was observed from the study that the drug release from the test formulation could be sustained and it was concluded that the test formulation was able to sustain the drug release as compared to reference marketed product with 1.672 fold increase in extent of absorption i.e., AUC_{0-t}.

Keywords: buccal delivery, Isradipine, bioadhesion, photostability, bioavailability

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INTRODUCTION

In recent years there has been increasing interest on the use of bioadhesive polymers to control the delivery of biologically active agents. Buccal delivery of drugs is one of the alternative to the oral route of drug administration. High first pass metabolism, and drug degradation in the harsh gastrointestinal environment, can be circumvented by administering the drug via the buccal route. Moreover, buccal drug delivery offers a safer method of drug utilization. Since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal delivery[1]. Buccal drug delivery is most advantageous because of abundant blood supply in buccal mucosa, bypassing the hepatic first pass effect and accessibility[2].

Isradipine, 4-(4-Benzofurazanyl)-1-4-dihydro-2,6-dimethyl-3-5-pyridinedi-carboxylic acid methyl-1-methylethyl ester is a potent dihydropyridine calcium antagonist used for treatment of hypertension and stable angina pectoris[3,4]. It is insoluble in water and the chemical formula $C_{19}H_{21}N_3O_5$ represents a molecular weight of 371.38. Cyclodextrins (CDs) are cyclic oligosaccharides consisting of usually six, seven, or eight glucose units (α-, β- and γ CDs, respectively) bound by 1,4-glycosidic linkages[5]. CDs are known to form inclusion complexes with hydrophobic drugs and improve their water solubility, dissolution rate and bioavailability[6,7]. Here β-Cyclodextrin (βCD) is used to improve the solubility and photostability of the drug. Isradipine is 90-95% absorbed and is subject to extensive first-pass metabolism, resulting in a bioavailability of about 15-24%[8]. Isradipine dosing guidelines generally call for a dose of 2.5 mg as an immediate release capsule orally twice a day and as controlled-release tablets of 5 mg orally once a day. The maximum recommended daily dose for both immediate and controlled release dosage forms is 20 mg/day although most patients show no additional response to doses above 10 mg/day with many side effects. The above mentioned limitations of oral administration make buccal route a suitable alternative for the systemic delivery of Isradipine, leading to improved bioavailability and reduction in dose dependent side effects[9].

MATERIALS AND METHOD

Materials

Isradipine was received as gift sample from Matrix Laboratories Limited (Hyderabad, India). HPMC K4M (Hydroxy Propyl Methyl Cellulose), Carbopol 971P, Sodium CMC and βCD were gifted by Dr Reddys Laboratories, Hyderabad, India. Isradipine tablets USP (Cobalt laboratories USA) All reagents used were of analytical grade.

Methods

Formulation Development of Isradipine buccal tablets

Mucoadhesive buccal tablets of IDP were prepared by direct compression of the drug or drug-βCD complex with mucoadhesive polymers using 8 mm flat punches and corresponding dies on 16 station rotary compression machine (Riddhi, Ahmedabad, India) (Table 1). HPMC K4M, Carbopol and Sodium CMC were used as mucoadhesives, sodium stearyl fumerate (SSF) as lubricant and pearlitol as filler. IDP was first mixed with the buccal mucoadhesive polymer mixture for 10 min in a mixer (VJ Instruments Ltd, Mumbai, India). Perlitol and SSF were then added, and mixing continued for another 10 min. The machine was adjusted to produce tablet weight of 115 mg. Formulation and *ex vivo* evaluation of Isradipine buccal tablets was discussed in our previous publication[10].

Table 1: Composition of Isradipine buccal tablets

Formulation	Drug	β-Cyclodextrin	Inclusion complex	HPMC K4M	Carbopol 974P	Sod CMC	Filler (Perlitol SD 200)	SSF
FH1	5	-	-	10	-	-	98	2
FH2	5	-	-	20	-	-	88	2
FH3	5	-	-	30	-	-	78	2
FH4	5	31	-	20	-	-	57	2
FH5	-	-	31	20	-	-	62	2
FC1	5	-	-	-	5	-	103	2
FC2	5	-	-	-	10	-	98	2
FC3	5	-	-	-	15	-	93	2
FC4	5	31	-	-	10	-	67	2
FC5	-	-	31	-	10	-	72	2
FS1	5	-	-	-	-	20	88	2
FS2	5	-	-	-	-	30	78	2
FS3	5	-	-	-	-	40	68	2
FS4	5	31	-	-	-	30	47	2
FS5		-	31	-	-	30	52	2

All values represented in mg/tablet

***In vivo* Pharmacokinetic studies of Isradipine buccal tablets in healthy human volunteers**

The bioavailability study in healthy human volunteers was conducted with permission from Ethical Committee, University College of Pharmaceutical Sciences, Kakatiya University, Warangal (Letter No. UCPSc/KU/BA/2012-17). Isradipine concentrations in plasma samples were determined by reported HPLC method with slight modifications[11].

Subjects

Eight healthy male volunteers, aged between 24-26 years and weighing between 63-72 kg participated in the study (Table 2). All the volunteers were healthy and were explained about the study design, drug pharmacokinetics and pharmacodynamics along with the probable adverse effects or side effects. The subjects were non smokers and were not taking any kind of medication before and during the study. The informed consent was obtained from each of them.

Table 2: Demographic description of subjects involved in bioavailability study

S.No	Volunteer Code	Age (Years)	Sex	Height (cm)	Weight (kg)
1	A	24	M	165	63
2	B	25	M	165	70
3	C	25	M	160	70
4	D	24	M	165	64
5	E	26	M	170	72
6	F	25	M	175	67
7	G	24	M	165	65
8	H	25	M	160	64

Study products

The test product was Isradipine buccal tablets (F3) which contains Isradipine equivalent to 5 mg. The reference product was immediate release Isradipine tablets USP (Cobalt laboratories USA). *In vitro* release profile studies were conducted in pH 6.6 buffer for test and reference product.

Study Design

This study was performed in a two-way crossover design with a washout period of 15 days between two phases. All the volunteers were subjected to overnight fasting before drug administration. No other drugs were taken during the study period. The subjects were randomly divided into two groups, the optimized test formulation containing 5 mg of Isradipine was placed in the buccal region to one group and Isradipine tablets USP was administered to another group in first phase. In second phase vice versa followed after 2 weeks of wash out period. Blood samples were collected at preset time intervals of 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hrs.

Estimation of drug in Plasma by HPLC Method

Chromatographic conditions for Isradipine estimation in human plasma

System : Shimadzu LC-20AD (UV-Visible Detector)

Analytical column : C18 RP Grace (25 cm X 4.6 mm ID, particle size 5 µ)

Wavelength : 325 nm.

Sensitivity : 0.001 AUFS.

Mobile phase : Acetonitrile : water (pH is adjusted to 4 by acetic acid) (50:50)

Flow rate : 1.3 mL / min.

Internal standard : Diazepam

Estimation of drug in plasma

A series of plasma samples containing 1, 5, 10, 15, 20, 25, 30 and 35 ng/mL of Isradipine was prepared to study the relationship between the ratio of peak area of drug to Internal standard and the concentrations of drug under selected conditions (Figure 1)

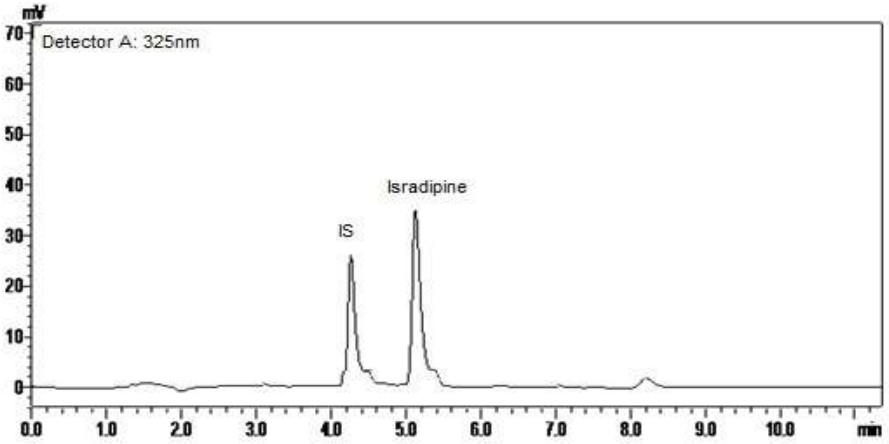

Figure 1: A typical chromatogram of Isradipine (RT 5.2 min) and Internal standard (RT 4.31 min)

Sample treatment

To a 0.25mL plasma previously spiked with the drug, 10 µL (100 ng/mL) internal standard and 0.5mL acetonitrile were added. The mixture was vortexed for 2 min and then centrifuged at 4000 rpm for 3 min. A 50 µl aliquot was injected into the column. Peak area and peak height were recorded in each case to construct the calibration curve. The concentration of *in vivo* samples was calculated from the equation using regression analysis, Y = mX+C, where X = Concentration of Drug, Y = Peak ratio of Drug/IS, m = solpe of the calibration curve and C = intercept of calibration curve.

Ex vivo and in vivo correlation between in vitro % drug release and area under curve

The cumulative percentage of Isradipine permeated *ex vivo* from the buccal tablet was compared against the extent of absorption i.e., cumulative AUC values for a possible *ex vivo – in vivo* correlation.

RESULTS AND DISCUSSION

Any one can find the discussion for evaluation of buccal formulations for in vitro release, moisture absorption, mechanical properties and bioadhesion in our previous publication[10].

***In vivo* Pharmacokinetic studies of Isradipine in healthy human volunteers**

The individual and mean (±SD) plasma concentrations of Isradipine were determined at different time intervals following oral and buccal administration of reference and test product respectively. Standard curve for the determination of drug in plasma by HPLC method shows y=0.036x+0.015 and regression value (r^2) of 0.973.

The pharmacokinetic parameters C_{max}, t_{max} and AUC_{o-t} of test formulation were calculated and compared with the reference i.e., marketed product (Table 3). It was observed from the study that the drug release from the test formulation could be sustained and it was concluded that the test formulation was able to sustain the drug release as compared to reference marketed product with 1.672 fold increase in extent of absorption i.e., AUC_{0-t}.

The Cmax, tmax, and AUC_{0-t} obtained with test and reference marketed product when studied with paired t test showed significant difference ($P<0.05$) between the two formulations. This difference may be due to the reason that one product is administered as immediate release tablet and other as buccal sustained release formulation. Thus the bioavailability improved considerably compared to marketed product (Figure 2)

Table 3: Pharmacokinetic Parameters of Isradipine administered as reference and test products

Formulation	C_{max} (ng/mL)	T_{max} (h)	$T_{½}$ (h)	MRT	AUC_{0-t} (ng-h/mL)	AUC_{total} (ng-h/mL)
Ref	11.289	1.5	2.26	3.633	36.917	40.364
Test	7.356	6	5.794	11.137	61.73	93.08

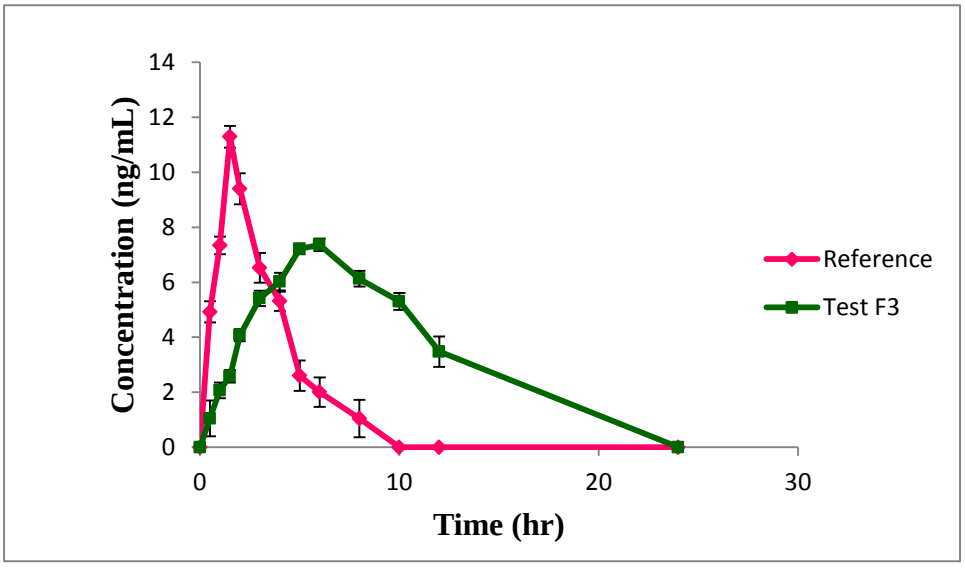

Figure 2: Plasma concentration of Isradipine in reference and test product in healthy human volunteers

***Ex vivo-In vivo* correlation between % drug permeated and AUC**

As per the biopharmaceutical classification system, Isradipine is a drug which has high solubility and low permeability. i.e. BCS class II drug. *Ex vivo - in vivo* correlation was carried out by plotting the *ex vivo* % drug permeated from the FS5 and AUC obtained after administration of buccal tablet is presented in the figure 3. A fairly good correlation was observed with $r^2 = 0.946$.

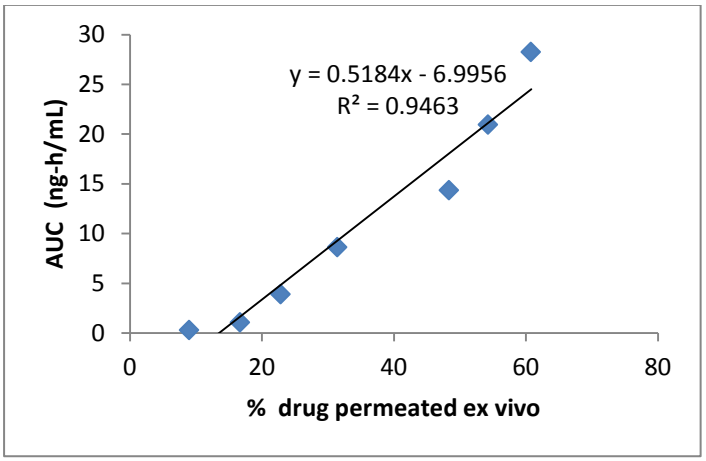

Figure 3: *Ex vivo – in vivo* Correlation of Isradipine between % drug permeated and AUC

CONCLUSION

The inclusion complex of Isradipine and β-cyclodextrin would be useful for enhancing the solubility of poorly water-soluble Isradipine. The DSC and *XRD* results confirmed the change to amorphous Isradipine. The photostability test revealed that, the inclusion complex was more stable than the raw Isradipine in the light [10]. Based on these previous results, the bioavailability study was carried out with optimized formulation. The study also established the fact that the developed test formulation was effective and better than the marketed dosage form of the tablet. Higher bioavailability, with same dose and showing sustained effect can be considered as better product.

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