Research Article



Formulation and Evaluation of Fast Dissolving Mucoadhesive Buccal Films of Candesartan Cilexitil using Factorial Design

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Received: 10-05-2017; Revised: 06-07-2017; Accepted: 25-07-2017.

ABSTRACT

The purpose of this investigation was to develop fast dissolving muco-adhesive buccal films of Candesartan cilexetil by solvent casting technique to deliver candesartan into blood via buccal mucosa and to show immediate action using jack fruit gum as novel muco-adhesive polymer. A 2² factorial design was considered in optimizing the formulation by taking Jack Fruit Gum (JFG), muco-adhesive polymer and Hydroxy Propyl Methyl Cellulose (HPMC), film forming polymer as two independent variables at two levels (high and low). The response factors considered were tensile strength, bio adhesion force and drug release. DSC analysis revealed no interaction between drug and polymers. Ex vivo diffusion studies were carried out using Franz diffusion cell, while bio adhesive properties were evaluated using porcine buccal mucosa as model tissue. Results revealed that bilayer film containing 0.1% (w/v) JFG and 0.6% (w/v) HPMC in the drug layer and 1% (w/v) ethyl cellulose in backing layer demonstrated diffusion of 94.12% through the porcine buccal mucosa. Thus, this study suggests that Jack fruit gum can act as a potential mucoadhesive polymer for buccal delivery of antihypertensive drug candesartan cilexitil.

Keywords: 3D surface plots, buccal film, quality by design, candesartan cilexitil, and Jackfruit gum.

INTRODUCTION

ast dissolving delivery systems are gaining much more importance now a day as they offer immediate relief from serious conditions.¹ Buccal route is preferred mostly for the drugs which have poor solubility, dissolution and bioavailability and for the drugs which show high hepatic first pass metabolism. Buccal route is the most convenient route as it is noninvasive and more patient compliance. This is because the buccal mucosa is highly vascularized and the drugs are directly absorbed into blood stream and shows immediate action. Moreover this route can be used for local and systemic effects.^{2, 3, 4} As the drug directly reaches the blood, the dose can be minimized. Several buccal adhesive delivery devices have been developed such as tablet, wafers, gels and films. Overall, a muco-adhesive buccal film offers several benefits due to its small size, thickness and improved patient compliance compared to tablets and gels. Buccal films offer more surface area and offers rapid disintegration and rapid absorption.⁶The muco-adhesive buccal films adhere to the buccal mucosa and then the films are disintegrated after hydrating in saliva and release the drug. As the film adhered to buccal mucosa the released drug has more chances to get fastly absorb into the blood stream through mucosal layer.

Candesartan is an angiotensin receptor blocker which was commonly used to treat hypertension. It is a BCS Class II drug with 15% oral bioavailability due to its poor solubility.⁷So in the present study an attempt was made to formulate candesartan fast dissolving buccal films by solvent casting technique to improve its bioavailability and to have fastest onset of action. There are several methods to formulate buccal films, solvent casting technique is one of the most common and simplest methods.

Natural polysaccharides have been widely used as bioadhesive polymers because of their biocompatibility and biodegradability properties. In this study, Jack Fruit Gum (JFG), a polysaccharide extracted from the pulp of *Artocarpus heterophyllus* Lam., family Moraceae was used for muco-adhesion.

An attempt has been made in the present investigation to utilize JFG, which is abundantly available and a cheap source of polysaccharide in formation of a buccal film of Candesartan cilexitil. Thus, the aim of this work was to develop and characterize a fast dissolving muco-adhesive buccal film of candesartan cilexitil using natural polysaccharide JFG.

MATERIALS AND METHODS

Materials

Candesartan cilexitil was obtained as a gift sample from Natco pharma Ltd. (Hyderabad). Hydroxy Propyl Methyl Cellulose (HPMC) purchased from Noveon Inc. All other chemicals and solvents used were of analytical grade.

Experimental design

A 2² randomized full factorial design was used for optimization of buccal films. In this model two factors were evaluated, each at two levels (high and low levels). The concentrations of muco-adhesive polymer (JFG), and Film Forming Polymer (HPMC) were selected as independent variables. Tensile strength (Y1), bio-adhesion



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force (Y2) and % drug release at 40 min (Y3) were selected as response factors.

Compatibility of drug and excipients

FTIR Analysis

The binary mixtures of drug and various excipients like jackfruit gum, HPMC E 50, used in formulations were analyzed by FTIR (Shimadzu- FTIR- 460 plus) for determination of interactions. Drug was mixed with excipient in 1:1 ratio and samples were stored for 30 days at 40 \pm 2°/75 \pm 5%RH. FT-IR spectra of these samples were then obtained after 30 days.

DSC analysis

The compatibility of drug with excipients was also analyzedusing Differential Scanning Calorimetry by placing the sample in a DSC crucible, sealed and then analyzed.

Preparation of muco-adhesive buccal films

Muco-adhesive buccal films were prepared by solvent casting method. JFG and HPMC were soaked in 15 ml water for 4 hrs and then candesartan cilexitil was dispersed in it. To this aspartame and propylene glycol were added and stirred on magnetic stirrer for 30 min and then sonicated for 30 min. The solution was poured in Petri plate of size 7.7 cm in diameter and was dried in vacuum oven at 50° C for 24 h. The backing layer was prepared by ethanolic solution of ethyl cellulose (1%, w/v). The homogenous solution was poured on the dried medicated film. It was dried in vacuum oven at 50° C for 5 h. The dried bilayer films were cut into square pieces of sides 1 cm containing 8 mg of drug per patch. **Table 1** shows the composition of formulated buccal films.

Characterization of buccal films

Thickness and weight

Screw gauge was used to measure the thickness of films. Three films, each of 1 cm^2 surface area were randomly selected and weighed. Then the average weight of the film was calculated.

Measurement of surface pH

Surface pH of film was determined to check whether the film causes irritation to the mucosa. The surface pH of randomly selected 3 films were measured using pH meter (Equip-Tronics, EQ-614, India) by placing the probe in close contact with the wetted film surface.⁸

Folding endurance

Number of times a film can be folded at the same place without breaking or cracking gives the value of folding endurance. This was determined by repeatedly folding the films at the same place until they broke or were folded for 300 times which ever is less.⁹

Ex Vivo Muco adhesion Study

Muco adhesive strength of all fabricated buccal patches was measured *ex vivo* (n = 3) on a modified physical balance using the method described by Gupta *et al.*¹⁰ A piece of porcine buccal mucosa was tied to the open mouth of a glass vial filled completely with isotonic phosphate buffer, pH 6.8. The glass vial was tightly fitted in the center of a beaker filled with isotonic phosphate buffer (pH 6.8; temperature, $37 \pm 1^{\circ}$ C). The patches were stuck to the lower side of the rubber stopper with glue. The mass (in gram) required to detach the patches from the mucosal surface gave the measure of muco adhesive strength (shear stress). The following parameters were calculated from muco adhesive strength⁴:

Force of adhesion (N) =
$$\frac{\text{Mucoadhesive strength}}{1,000} \times 9.81$$
-----(1)

Bond strength
$$(Nm^{-2}) = \frac{\text{Force of adhesion}}{\text{Surface area}}$$
-----(2)

In vitro release of candesartan cilexitil from buccal film

The commercially available dialysis membrane (obtained from Sigma Chemicals) was employed for the study, and the in vitro drug release study was carried out using a Franz diffusion cell.¹¹The effective diffusion area was 1.8 cm². The receptor compartment (40 ml) was filled with phosphate buffer saline (PBS), pH 6.8. The patches were fitted between the donor and receptor compartments of the diffusion cell. The drug release was performed at 37±0.5°C, at a stirring speed of50 rpm using a magnetic stirrer. Five milliliters of the sample from receptor medium was withdrawn at regular intervals and replaced immediately with an equal volume of phosphate buffer saline, pH 6.8. The amount of candesartan released into the receptor medium was quantified by using UV–visible spectrophotometer at 238 nm against a blank.

Ex vivo permeation studies

Ex vivo permeation study of film was carried out on Franz diffusion cells of diffusional diameter 1.76 cm and volume of 7 ml which were placed on six station magnetic stirring unit (Whirlmatic, Spectralab, India) using porcine buccal mucosa. The diffusion was carried out with Phosphate buffer pH 6.8 as receptor media maintained at $37 \pm 5 \circ C$ and was continuously stirred at 300 rpm with the help of a tiny teflon coated needle shaped magnetic. The diffusion was carried out for 30 min. Samples were withdrawn at predetermined time intervals of 5, 10, 15, 20, 30 min. At each time 0.5 ml samples were withdrawn and replaced with fresh phosphate buffer pH 6.8. These aliquots after centrifugation were diluted appropriately and analyzed using UV spectrophotometer (1800, Shimadzu, Japan) at 238 nm.^{12, 13}



International Journal of Pharmaceutical Sciences Review and Research

256

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Stability studies

Films of formulae F3 were wrapped in a butter paper followed by aluminum foil and kept in an aluminum pouch which was heat sealed at the end and Stored at 30°C and 60% relative humidity. The films were evaluated periodically for percent drug content and time to dissolve the film. Stability studies were carried out for a period of 3 months.

RESULTS AND DISCUSSION

Experimental trials were performed for all 4 possible combinations by 2^2 randomized full factorial designs by using Design Expert software. Mathematical relationships generated for the studied response variables are expressed as **Equations (3-5).** The formulation layout for the factorial design batches F1–F4 is shown in **Table 1**.

Table 1: factorial design, composition and different parameters of the corresponding 4 formulations

Formul	Variable levels in coded form		Ingredients				Bioadhesi- on force	Tensile strength	Drug release (%)after		
ation	НРМС	JFG	Candesartan cilexitil	нрмс	JFG	Propylene glycol	Aspart- ame	Water	(N)±S.D	(N/m²)±S.D	20 min±S.D
F1	-1	-1	8 mg	0.2 % w/v	0.1 % w/v	1.5 % w/v	0.125 % w/v	Q.S	0.15± 0.03	83.33± 0.14	84.23± 0.5
F2	-1	+1	8 mg	0.2 % w/v	0.5 % w/v	1.5 % w/v	0.125 % w/v	Q.S	0.28± 0.02	155.56± 0.08	78.29 ± 0.6
F3	+1	-1	8 mg	0.6 % w/v	0.1 % w/v	1.5 % w/v	0.125 % w/v	Q.S	0.20± 0.03	111.11± 0.04	95.48± 0.4
F4	+1	+1	8 mg	0.6 % w/v	0.5 % w/v	1.5 % w/v	0.125 % w/v	Q.S	0.19± 0.01	105.56± 0.11	86.86± 0.8

Ethyl cellulose (1%, w/v) Backing layer on F1–F4 formulations

Compatibility of Drug and Excipients

FTIR analysis

FTIR analysis of pure drug and drug and excipients were shown in Figures 1(a)-(c). The FTIR studies do not reveal any additional peak for the drug, indicated that the drug did not interact with excipients used in the films. The pure drug Candesartan cilexetil showed characteristic absorption at 2941 cm-1, 1752cm-1, 1714cm-1, 1613 cm1. This absorption peak at 2941 cm-1 was due to stretching of C-H bond, the peaks at 1752cm-1 and 1714cm-1 were due to two C-O bonds (carbonyl group) and peak at 1614 cm-1 was due to C-N bond. Figure – 1(a) shows IR scan of pure drug and Figure 1(b) and 1(c) shows IR scan of pure drug with the jackfruit gum and HPMC E50 respectively, from the figures it was confirmed that there were no drug-Excipient interactions.



Figure 1: FTIR of (a) pure drug (b) pure drug and jack fruit gum (c) Pure drug and HPMC E 50

DSC of (d) pure drug (e) pure drug and jack fruit gum (f) pure drug and HPMC E 50

DSC analysis

The DSC of pure drug has a peak at $175^{\circ}C$ and the drug with all the excipients has also shown the peaks in between $170-175^{\circ}C$. Thus, it confirms that the excipients

used were compatible with the drug and can be used for further formulations. The DSC peaks of pure drug, pure drug with jack fruit gum and pure drug with HPMC E 50 were shown in figures 1(d)-(f) respectively.



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Characterization of buccal film

Thickness and weight

The average thickness of all prepared buccal films ranged from 0.21 to 0.27 mm. Weight variation values (g) of film (1 cm^2) for formulations F1 to F4 were found to be between 0.4 and 0.7g. As the thickness of the films increases, proportional gain in weight of films was observed. This depicts uniform film casting.

Measurement surface pH

Surface pH for formulation F1–F4was found to range from 6.65 to 6.92 which were in the range of salivary pH (6.5–7.2). Thus, no mucosal irritation was expected.

Folding endurance

As the film forming polymer concentration increases there observed an increase in folding endurance. Folding endurance values for films indicates high mechanical strength of these films. This is highly desirable because it would not allow easy dislocation of the films from the site of application or breaking of film during administration.

Effect of formulation variables on in- vitro bio-adhesion force

This is an important property as it ensures delivery of drug at the site of administration. The bio adhesion force was found to increase with increase in concentration of jack fruit gum and decrease in concentration of HPMC.

The polynomial equation for R1 (Bio adhesion force) in terms of coded and actual factors were given in equations 1 & 2.

From the equations and the plots obtained it was clear that HPMC and HPMC-JFG combination has negative effect and JFG has positive effect on bio adhesion force. Bio adhesion Force of buccal films increases with increase in jack fruit gum concentration and decreases with HPMC. The half normal and 3D surface plots for the factor bio adhesion force were given in Figures 2(a) and 2(b) respectively.

R2=+113.89-5.55*+16.67*B-19.45*AB-----eq(3)

Final Equation in Terms of Actual Factors:

Tensile

strength=+41.66000+118.06250*HPMC+277.80000*JFG-

486.12500*HPMC*JFG----- eq (4)

Effect of formulation variables on in vitro release of candesartan cilexitil from buccal film

The polynomial equation for R3 (drug release) in terms of coded and actual factors were given in equations 5 & 6.

From the equations and the plots, it was clear that JFG and HPMC-JFG combination has negative effect and HPMC has positive effect on bio adhesion force. The

cumulative percentage release increased with increase in concentration of HPMC.

The half normal and 3D surface plots for the response factor tensile strength were given in **Figures 2(e) and 2 (f)** respectively.

Final Equation in Terms of Coded Factors:

R3=+86.22+4.95*A-3.64*B-0.67*AB------ eq (5) Final Equation in Terms of Actual Factors:

Drug release=+79.75500+29.80000* HPMC-11.50000* JFG-16.75000* HPMC *-----eq (6)



Ex vivo permeation studies

The permeation profiles of can desartan across porcine buccal mucosa were shown in Table 3. Films containing higher percentage of HPMC provided greater amount of permeated drug than other formulations. Formulation F3 showed highest diffusion of around 94% at the end of 30 min. The tensile strength and bio adhesion force were also higher for F2 and F3 formulations compared to other formulations.

In-vitro drug release studies

This observation can be correlated with in vitro drug release profiles, which influences drug availability at the absorption site. Though both F2 and F3 showed better tensile strength and bio adhesion force, F3 was selected as optimized formula due to more drug release than F2.The higher drug release and thus higher permeation of F3 may be due to presence of higher amount of water soluble film forming polymer HPMC. The formulation F4 also contained higher concentration of HPMC but the release was less because it also contained higher amount of water insoluble mucoadhesive polymer jack fruit gum



Available online at www.globalresearchonline.net © Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited. which may retard the drug release from the formulation. *In-vitro* drug release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetics and according to Higuchi and Peppas models to ascertain mechanism of drug release. From the

results, which were shown in Table 4 it was evident that all the formulations displayed first order release kinetics. Higuchi and Peppas models reveal that drug release is by non-Fickian diffusion (n values from 0.55 to 0.88). The plots were shown in the Figures 3(a)-(d).

Fable 3: physicochemica	l characteristics	and Ex-vivo	permeation	data of the film
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Formulation	Thickness (mm) ±S.D	Weight uniformity (g) ±S.D	Surface pH ±S.D	Folding endurance ±S.D	Permeation studies (%) ±S.D
F1	0.21 ± 0.063	0.49 ± 0.006	6.82 ± 0.54	185 ± 1.02	83.15 ± 0.2
F2	0.23 ± 0.076	0.58 ± 0.005	6.65 ± 0.48	190 ± 1.24	79.32 ± 0.6
F3	0.25 ± 0.053	0.59 ± 0.005	6.7 ± 0.60	179 ± 1.13	94.12 ± 0.1
F4	0.27 ± 0.067	0.69 ± 0.006	6.92 ± 0.52	199 ± 1.31	85.09 ± 0.4

Table 4: Release	kinetics	of various	formulations
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Formulation	Zero Order Plot R ²	First Order R ²	Higuchi Plot R ²	Peppas Plot R ²	Peppas Plot n value
F1	0.967	0.991	0.938	0.965	0.62
F2	0.974	0.994	0.933	0.972	0.55
F3	0.936	0.976	0.953	0.955	0.88
F4	0.963	0.989	0.943	0.969	0.71





Figure 3: (a) Zero order plot (b) First order plot(c) Higuchi plot (d) Peppas plot

Optimization

The computer optimization technique by the desirability approach was used to produce the optimum formulation. The process was optimized for the response variables R1–R3. The optimized formula was arrived by setting maximum percentage drug release at 20 min with a better bio adhesion force and tensile strength. Formulation F3 was found to be optimized formulation.

Stability studies

The films did not show any statistically significant change in appearance, % drug content, and disintegration time on storage. The % drug content and disintegration responses were same as that of the responses before the storage. This indicated that F3film was stable after storage.



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CONCLUSION

In the present study, fast dissolving mucoadhesive buccal film of candesartan cilexitil were prepared using jack fruit gum and hydroxyl propyl methyl cellulose, which released the drug within 20 min, which would prevent first-pass metabolism to a large possible extent.

Bilayer films were prepared by 2^2 level factorial design and effect of formulation variables on drug release, bio adhesion force and tensile strength were analyzed by applying the computer optimization technique. Based on the results for dependent variables, formulation F3 was found to be optimal formulation.

Thus, an attempt of formulating a stable fast dissolving mucoadhesive buccal film of candesartan for treatment of hypertension using novel polysaccharide polymer jack fruit gum was made by optimization technique. Jack fruit gum showed good bio adhesion along with film forming polymer HPMC. Thus, cheap and abundantly available natural polysaccharide JFG could be a promising vehicle for systemic delivery of drugs like candesartan cilexitil through buccal route.

The in vitro studies have shown that this is a potential drug delivery system for candesartan with considerable release profile. But, in vivo studies in future would be needed to confirm these results.

Acknowledgement: The authors are thankful to University College of pharmaceutical sciences, Acharya Nagarjuna University, for providing necessary facilities to carry out this research work.

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Source of Support: Nil, Conflict of Interest: None.



260

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