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DESIGN, FORMULATION, AND EVALUATION OF LISINOPRIL MUCOADHESIVE BUCCAL PATCHES BY USING THE COMBINATION OF NATURAL POLYMERS

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Abstract

The main objective of present investigation to formulate and evaluate mucoadhesive buccal patches of Lisinopril using solvent casting method. Sodiumalginate combined with Sodium carboxyl methyl cellulose, HPMC, and Carbopol934 in different proportions were used as a mucoadhesive polymer and Propyleneglycol used as a plasticizer as well as penetration enhancers. The formulated Buccal patches of Lisinopril were evaluated on the basis of Thickness, Weight uniformity, folding endurance, swelling Studies, Surface pH Determination, Percentage Moisture loss, Drug content Uniformity, Ex-Vivo Mucoadhesive strength, In Vitro Drug Release, Ex- vivo permeation study. By compatibility study there is no chemical interaction between drug and excipients used. All prepared buccal patches were transparent, smooth, consistent and flexible. The surface pH of all formulations was found to be almost in neutral pH and no mucosal irritation was expected. Among all the formulations, F6 showed maximum swelling index as 25.01%. The optimized formulation F6 also showed satisfactory, Mucoadhesive strength (5.1kg/cm2), drug content (98.75), and Ex-Vivo permeation (82.03%). In-Vitro drug release of optimised formulation (F6) was found to be 75.12 at the end of 8 hrs. Drug release mechanism was determined by plotting release data to Higuchi and Korsmeyer-Peppas model. All the formulations are best fitted to Korsmeyer-Peppas model and according to this model the drug releases from theses patches may be controlled by diffusion with super case-II transport.

Keywords: Buccal patches, Mucoadhesion, Lisinopril, *In-Vitro* Drug Release, *Ex-Vivo*permeation.

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Introduction

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient. However per oral administration of drugs has been associated with hepatic first pass metabolism and enzymatic degradation within the GI tract that prohibits oral administration of certain classes of drugs especially peptides and proteins [1]. Buccal delivery offer direct access to the systemic circulation through the external jugular vein thus bypassing the drugs from the hepatic first pass metabolism [2]. This may lead to higher bioavailability of such drugs. Buccal drug delivery involves the administration of desired drug through the buccal mucosal membrane, which forms the lining of the oral cavity. This route is useful for mucosal (local effect) and transmucosal (systemic effect) drug administration [3]. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa for local action, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation. The buccal mucosa permits a prolonged retention of a dosage form especially with the use of mucoadhesive polymers without much interference in activities such as speech or mastication unlike the sublingual route [4]. Lisinopril is an orally active non sulfhydryl angiotensin converting enzyme (ACE) inhibitor indicated for the treatment of patients with hypertension, heart failure or with acute myocardial infarction [5]. Lisinopril on oral administration undergoes extensive metabolism in the liver resulting into very poor (approximately 25%) bioavailability. In order to improve its bioavailability, efficacy and to minimize the side effects associated with oral administration, mucoadhesive buccal films of Lisinopril using sodium alginate, sodium carboxyl methylcellouse, Hydroxypropyl methylcellouse, and Carbopol 934 were prepared by solvent casting technique in the present investigation [6].

2. Materials and Methods

Lisinopril was a gift sample from Dr. Reddy's laboratories, Hyderabad. Sodium alginate, sodium carboxyl methyl

cellouse, Hydroxypropyl methylcellouse, and Carbopol 934 were obtained from Bross chemicals Tirupati;other chemicals used were of analytical grade.

3. Preparation of mucoadhesive buccal patches

Solvent casting was used wherever possible in the development of Buccal Patches. Dissolved in distilled water, the necessary polymer amount was added gradually and well blended. Tiny amounts of the drug were dissolved in that mixture. Add plasticizer to the aforementioned mixture and stir until combined. The petridishes were filled with the solution, and the oven was set to 40^{0}C to dry the contents. After 24 hours in a desiccator, the patches were removed using a sharp blade and then sliced to the proper size and form [7]. The composition of Lisinoprilbuccal patches represented in table 1.

Table.1: Composition of Lisinopril buccal patches

Formulation	Lisinopril (mg)	SA (mg)	HPMC (mg)	CP 934 (mg)	NaCMC (mg)	Propylene Glycol %	Distilled Water
F1	50	900	100	-	-	10	40
F2	50	700	300	-	-	10	40
F3	50	900	-	100	-	10	40
F4	50	700	-	300	-	10	40
F5	50	700	200	100	-	10	40
F6	50	600	100	300	-	10	40
F7	50	700	200	-	100	10	40
F8	50	600	100	-	300	10	40

4. Evaluations of Developed Film

4.1 Compatibility of Lisinopril with excipients

FT-IR spectra for pure Lisinopril and Different polymers acquired at room temperature using FT-IR spectrophotometer (FTIR-8400S, Shimadzu, Japan) in transmittance mode. The samples were ground in a mortar, mixed with Nujol and placed between two plates of KBr and compressed to form a thin film [8]. The sandwiched plates were placed in the infrared spectrometer and the spectra were obtained. Scanning was performed between wave numbers 4000-400 cm-1.

4.2 Differential scanning Calorimetry analysis

Method for estimating the physical interaction between drug and polymers used for the formulation of different dosage form is thermal analysis by DSC [9].

4.3Appearance

The formulated buccal patches visually observed for their color and transparency, Surface texture, by simply touching the surface of the formulated buccal patch the surface texture can be evaluated

4.4Folding endurance

Strip of prepared film (2 × 2cm) was folded repeatedly at the same place till it broke. The number of times the film could be folded at the place without breaking or cracking is equal to the value of folding endurance [10].

4.5Thickness (mm)

Films of (2×2 cm) were cut and the thicknesses of films were measured using micrometer screw gauge with at least count of 0.01 mm at five different spots of the films and average was taken [11].

4.6Weight variation

Weight variation was observed in films of 2×2 cm. ten films were weighed individually and average was taken.

4.7 Surface pH

Buccal films were left to swell for 1 hour on the surface of 2% agar plate; it was allowed to stand until it is solidified to form a gel at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen patch.

4.8 Tensile strength

The instrument used to measure the tensile strength designed in our laboratory especially for this project work. The instrument is a modification of chemical balance used in normal laboratory [12].

One pan of the balance was replaced with one metallic plate having a hook for attaching the film. The equilibrium ofthe balance was adjusted by adding weight to the pan of balance. The instrument was modified in such a way that the film can be fixed up between two hooks of horizontal beams to hold the test film. A film of 2.5 cm length was attached to one side hook of the balance and the other side hook was attached to plate fixed up to the pan.

$$T = \frac{M \times G}{B \times T} \text{ Dynes/Cm}^2$$

Where, T= force at break/ initial cross-sectional area of sample.

M = mass in grams

g = acceleration due to gravity 980 cm/sec^2

B = breadth of the specimen in cm

t = thickness of sample in cm.

4.9 Swelling index

Buccal film of 2 ×2cm area from each formulation was taken. Initial weight of the film was taken by using single pan balance ($w_1$gm) and it was placed in a petri dish containing 50 ml of water. After definite interval film was removed and blotted with filter paper and weighed again ($w_2$gm) [13,14].The swelling index was calculated from the formula,

$$\frac{W_2 - W_1}{W_1} \text{ X } 100$$

Where W_2 =wet weight of the film

W_1=dry weight of the film

4.10 Percentage Moisture content

The buccal films were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After three days, the films were taken out and weighed.

The %moisture content was determined by the formula [15].

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} X\ 100$$

4.11Drug content estimation

Prepared buccal film was dissolved in 100ml PBS of pH 6.8 using a magnetic stirrer for 12 hours and then sonicated for 30 minutes. The solution was centrifuged and then filtered. The drug content determination was done by using UV spectroscopy at 215 nm [16].

$$\% \text{ Drug content} = \frac{\text{Practical Loading}}{\text{Theoratical drug loading}} \text{ X } 100$$

4.12 In vitro drug release study

The USP dissolution test equipment (paddle technique) was used for the in vitro drug release experiments. Phosphate buffer (pH 6.8) was used to adhere a film with a 29mm diameter cutout to a glass slide. This slide was slanted at 45 degrees in a phosphate buffer pH 6.8 solution in a 1000 ml beaker. The dissolving media was kept at 37 ± 0.5º C with a constant stirring rate of 50 rpm. Samples were taken at regular intervals, and the dissolving medium was changed out for new ones. The samples were diluted with phosphate buffer to a pH of 6.8 and filtered using 0.45 m Whatman filter paper. The UV-VISIBLE spectrophotometer was used to determine the absorbance. Total medication release and percentage release over time were calculated [17-20].

4.13 Ex vivo permeation studies

The donor compartment of the 5.065 cm2 diffusion cell was fitted with an activated cellophane membrane and clamped with the receptor compartment, which was filled with PBS at pH 6.8. The magnetic stirrer was used to keep the temperature of the diffusion cell at 37 degrees. At 37^{0}C, a solution of the drug at a concentration of 1 mg/ml was constantly stirred before being withdrawn at regular intervals for spectrophotometric assessment and replaced by a new supply of receptor solution [21-25].

5. Results and Discussion

5.1 Compatibility of Lisinopril with excipients

The FTIR spectrum of Lisinopril and other excipients was shown in Figure 1 and the interpretations of IR frequencies were represented in Table 2.

The peaks in the FTIR spectrum of Lisinopril that correspond to the major functional groups are easily identifiable. The sample was proven to be Lisinopril since the primary peaks are chemically similar to the functional group of Lisinopril.

Table.2:The major peaks observed in FTIR spectrum of Lisinopril and Lisinopril with different polymers used in formulations.

Substance	WaveNo. (cm^{-1})	Functional group
Lisinopril	3065-3057	Aromatic C-H stretching
Lisinopril + Sodium alginate	2943-2925	Aliphatic C-H stretching
Lisinopril + HPMC	1652-1645	C-O stretching
Lisinopril + Carbopol934	1131-1125	C-F stretching
Lisinopril + Na CMC	837-982	C-H stretching

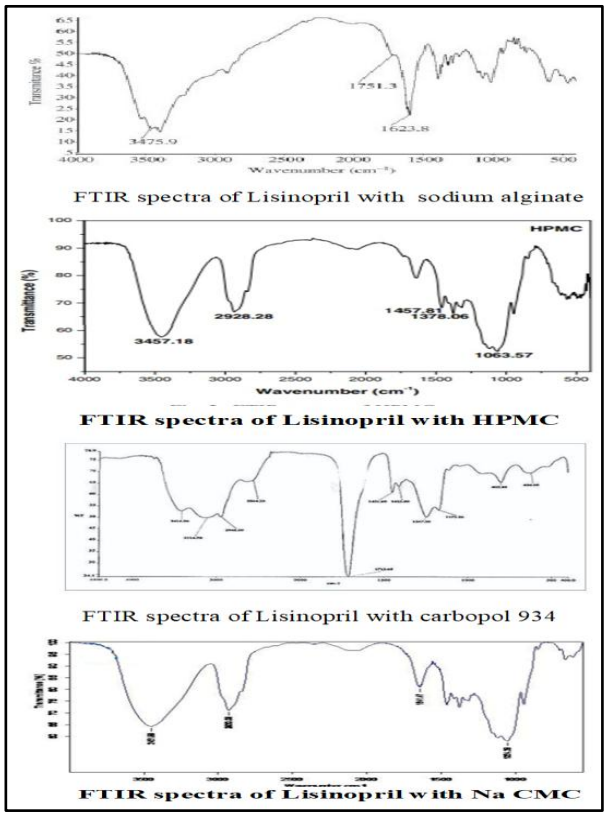

Figure.1: FTIR Spectrum of Lisinopril and excipients

5.2 Physical appearance and surface texture of patches:

Visual and tactile examination of patches served as the primary methods for verifying these values. The patches, as can be seen, have a sleek surface and a classy overall look.

5.3 Weight uniformity of patches

Uniformity of weight was calculated by weighing 5 patches and average was taken. Weight of the patches of formulation F1 to F8 varies from 25.00±1.73 to 47.66±0.57 mg, Results are tabulated in Table 3.

5.4 Thickness of patches

With the help of screw gauge thickness was measured and average was taken. Thickness of patches of formulation F1 to F8 varies from 0.52±0.01 to 0.58±0.05 mm. Results are

tabulated in 3. F8 formulation with polymer sodium alginate, HPMC, and Na CMC shows maximum thickness.

5.5 Folding endurance of patches:

Folding endurance of transdermal patch of formulation F1 to F8 ranges from 238±1.95 to 293.33±2.64. Formulation F6 with sodium alginate, HPMC, and Carbopol 934polymer has provided a greater number of folding without cracks as compared to other formulation. Results are tabulated in Table 3

5.6 Surface pH of patches:

The surface pH of the patches ranged between 5.76±0.11 and 6.46±0.05. The results were found to be close to neutral in all the formulations, and this means that they have less potential to irritate the buccal mucosa. Results were shown in the table 3.

Table.3: Physcial eveluation of mucoadhesive buccal patches of Lisinopril

Formulations	Average Weight (mg)	Average Thickness(mm)	Average Folding Endurance	SurfacepH
F1	35.76±2.13	0.55±1.06	264.13±2.53	6.41±3.01
F2	43.33±1.15	0.52±0.05	266.66±3.51	5.76±0.11
F3	33.33±1.15	0.58±0.01	243.33±2.08	6.46±0.05
F4	28.66±1.15	0.53±0.05	287.33±4.50	6.43±0.35
F5	25.00±1.73	0.57±0.05	249.66±2.08	5.8±0.37
F6	27.66±1.52	0.52±0.01	293.33±2.64	6.4±0.26
F7	45.66±1.52	0.54±0.05	238±1.95	5.76±0.15
F8	47.66±0.57	0.58±0.05	276.66±2.0	6.33±0.20

5.7 Drug content uniformity of patches:

Drug content of patch of formulation F1 to F8 ranges from 91.27±0.49 to 98.75±0.80 %. Formulation with sodium alginate, HPMC, and Carbopol 934polymer (F6) shows the maximum drug content. Results are tabulated in Table 4

5.8 In-vitro residence time of patches

n vitro residence time is one of the important parameter of buccal patches and the results are shown in the Table 4. The residence time of the formulations ranged between 5 hours to 7 hours twenty minutes. Out of all the formulations, formulation A12 showed highest in vitro residence time. n vitro residence time is one of the important parameter of buccal patches and the results are shown in the Table 4. The residence time of the formulations ranged between 5 hours to 7 hours twenty minutes. Out of all the formulations, formulation A12 showed highest in vitro residence time. in vitro residence time is one of the important parameter of buccal patches and the results are shown in the Table 4. The residence time of the formulations ranged between 5 hours to 7 hours twenty minutes. Out of all the formulations, formulation A12 showed highest in vitro residence time

In-vitro residence time is the one of the important parameter of buccal patches and the results are shown in table 4,the residence time of the formulations ranged between 3. 43 hours 43 min to 7 hours 15mins. Out of the all formulations F 6 showed highest in-vitro residence time. Results are tabulated in Table 4

Table.4: In-vitro residence time and drug content

Formulations	*In Vitro* Residence time (Hrs)	Drug Content Uniformity %
F1	3.43±0.12	93.38±0.27
F2	3.49±0.09	92.36±0.11
F3	4.24±0.13	94.01±0.40
F4	4.11±0.05	91.27±0.49
F5	6.47±0.15	96.79±0.07
F6	7.15±0.13	98.75±0.80
F7	5.24±0.11	92.95±0.11
F8	5.34±0.12	96.88±0.81

5.9 Ex-vivo permeation release

The Ex-vivo permeation release was observed and it improved with increasing concentrations of hydrophilic polymers. Maximum Ex-vivo permeation (75.21 ± 0.42%)during a 9-hour period was recorded for the formulation F6. Diffusion profiles for formulations F1-F8was visually shown in figure2. Response surface plot of SA and CP 934 on *Ex-vivo* permeation release shown on figure 3.

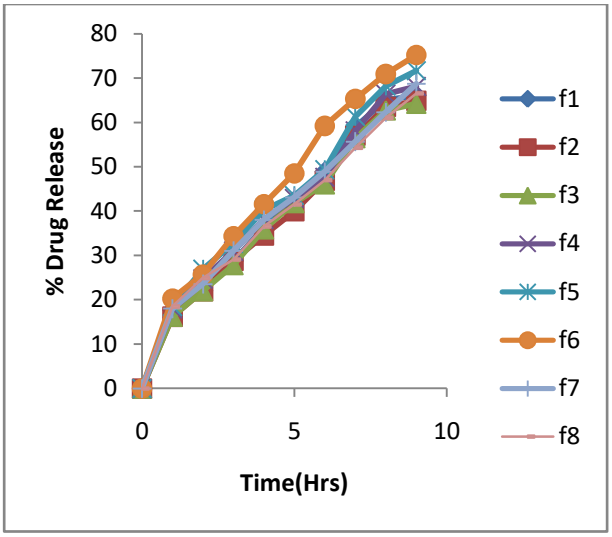

Figure.2: Comprehensive diffusion profile of formulations F1-F8

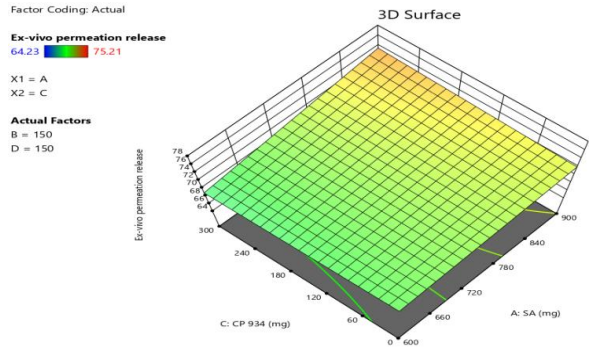

Figure.3: 3D Response surface plot of SA and CP 934 on Ex-vivo permeation release

5.10 In-vitro release

In vitro study on medication release from buccal patches showed some variation in drug and polymer characteristics. Concentrations of polymers with a higher hydrophilicity were shown to improve medication release from the buccal patches.Maximum in-vitro drug release (82.03 ±0.82 %)over a 7-hour period was seen in formulation F6 compared to all other formulations represented in table 5. In-vitro release profiles for formulations F1-F8 was visually shown in figure 3 and response surface plot of HPMC and CP 934 on in-vitro drug release profile shown in figure 4

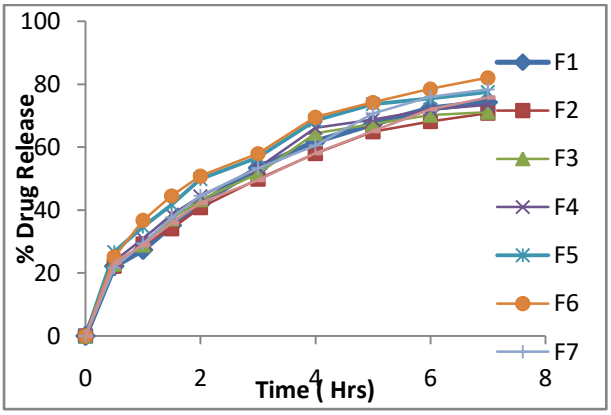

Figure.3:Comprehensive In-Vitro release profile of formulations F1-F8

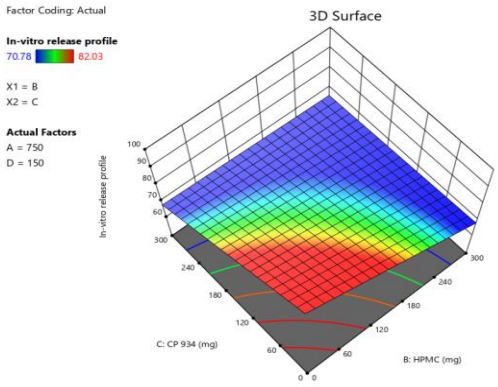

Figure.4:3D Response Surface plot of HPMC and CP 934 on *in-vitro* drug release profile

Table.5:*In-Vitro* drug release kinetics of formulations F1-F8

Formulation	Zero Order R^2	First order R^2	Higuchi R^2	Korresmayer Pappas		Best Fit model
				R^2	N	
F1	0.992	0.752	0.947	0.995	0.4539	Peppas
F2	0.990	0.766	0.928	0.993	0.4437	Peppas
F3	0.994	0.752	0.925	0.995	0.4002	Peppas
F4	0.989	0.832	0.958	0.993	0.4771	Peppas
F5	0.992	0.894	0.951	0.995	0.4226	Peppas
F6	0.993	0.872	0.928	0.994	0.4588	Peppas
F7	0.993	0.872	0.928	0.999	0.3744	Peppas
F8	0.998	0.841	0.909	0.991	0.3481	Peppas

6. Conclusion

FTIR studies revealed that there is no incompatibility or interaction between Lisinopril and excipients. Formulated buccal films gives satisfactory film characteristics like physical appearance, surface texture, weight uniformity, thickness uniformity, folding endurance, surface pH, percentage swelling index, percentage moisture uptake, drug content uniformity, in-vitro drug release. The low values for standard deviation for average weight,thickness, surface pH, percentage swelling index, percentage moisture uptake, in vitro drug release and drug content indicated uniformity within the batches. Lisinopril (50 mg), sodium alginate (600 mg), high-molecular-weight poly ethylene glycol (100 mg), and carbopol 934 (300 mg) were the active ingredients in the formulation F6 that demonstrated an acceptable and improved release profile, according to the research. Therefore, the optimal formulation was determined to be F6.The optimized formulation F6 followed zero order kinetics. Short term stability studies of optimized formulation as per ICH guidelines indicated that there is no significant change in physical appearance, drug content determination and in vitro drug release.

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