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Preparation and Evaluation of Buccal Mucoadhesive Tablets of Antihypertensive Drug

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A B S T R A C T

Buccal route of drug delivery has significant attention to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability. Such routes have expanded important notice due to their presystemic metabolism or instability in the acidic environment associated with the oral administration. Along with the variety of buccal layer mucosae of the oral cavity has convenient and easily effective site for the delivery of therapeutic agents. Lercanidipine a suitable candidate for buccal delivery. Hence, in this research work an attempt was made to formulate buccal tablets of Lercanidipine hydrochloride to increase patient compliance by reducing dosing frequency and to achieve plasma concentration profile over 12 h.

Keywords: Antihypertensive drug, buccal tablets, mucoadhesive tablets, suatained release, lercanidipine

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INTRODUCTION:

The buccal region is an attractive site for target-specific delivery of the active(s) on the mucosa for local and/or systemic effect by absorbing through the mucosal membrane barrier covering the oral cavity. In comparison to oral drug delivery, the mucosal lining of the buccal region has a few unique advantages [1]. It is highly vascularized and displays a decreased enzymatic activity, less sensitivity, ease of administration and expulsion of dosage form in the case of undesirable effects, avoiding acid hydrolysis of the stomach and bypassing hepatic first pass-effect. It enhances bioavailability of the drug hence requires a minimum dose and precipitates less dose related effects than other routes of administration. In addition, buccal administration exhibits better patient adherence in contrast to other non-oral drug-delivery routes. This route is excellent for potent drugs especially targeted for acute conditions with rapid clinical response due to direct access to the jugular vein and for extended therapeutic effect [2].

Traditional buccal dosage forms frequently fail to maintain desired drug concentration level either on the targeted mucosal site and/or in the systemic circulation. To sustain the therapeutic effect, it is essential to extend the intimate association between active(s) and the membrane barrier of buccal tissue [3]. To address these issues, buccal delivery system should be designed in such a manner to remain at the absorption site for desired duration of time, enhance the drug permeation across the mucosa to systemic circulation or into submucosal epithelial layers unaffected by the impact of salivary flow, pH, electrolytes, and mucosal enzymes [4]. The components in the buccal dosage forms are mainly classified as mucoadhesive polymers, penetration enhancers and enzyme inhibitors**.** Various mucoadhesive polymers have been investigated for prolonging the retention time of dosage forms or actives at targeted sites of oral mucosa. Buccal patches have gained tremendous attention in drug delivery owing to superior patient acceptance mainly contributed by ease of application, thinness and elasticity that induces only negligible discomfort to the patient [5]. Moreover, drug delivery via buccal mucoadhesive tablets have been the most commonly investigated dosage forms for buccal drug delivery. Several bioadhesive buccal tablet formulations have been developed by direct compression method in recent years either for local or systemic drug delivery. They are designed to release the drug either unidirectionally by targeting buccal mucosa or multi- directionally into the saliva. Alternatively, the dosage form can contain an impermeable backing layer to

ensure that drug is delivered unidirectionally. Disadvantages of buccal tablets may be patient acceptability (mouth feel, taste and irritation) and the nonubiquitous distribution of drug within saliva for local therapy. It is important to point out the possible problems those children and the elderly may experience by the use of adhesive tablets such as possible discomfort provoked by the material applied to the mucosa and the possibility of the separation of dosage form the mucosa, swallowing, and then adherence to the wall of the esophagus [6]. Hypertension is a medical condition where the blood pressure is chronically elevated is one of the commonly found diseases throughout the world. Lercanidipine belongs to the drug class known as calcium channel blockers. It relaxes and dilates the blood vessels thereby allowing blood to flow more freely throughout the body. Consequently, blood pressure is reduced and the heart is able to function more efficiently. The absolute bioavailability is reduced to approximately 10% because of extensive first pass metabolism to inactive metabolites. Mean half-live of Lercanidipine is about 4.4 h in humans after single dose of 20 mg. The primary aim is to protect the drug from an unfavourable environment in the gastrointestinal tract. The buccal route has long been advocated as possible route of delivery of drugs having poor oral bioavailability because of high first pass metabolism or degradation in the gastrointestinal tract [7]. The buccal mucosa reaching the heart directly via the internal jugular vein as this route is well vascularised with venous blood draining. Although, the drug fluxes via this route are less than that obtained with sublingual mucosa due to permeability barrier, the relative immobility of buccal musculature, as compared to that of sublingual route, makes this site ideally suited for delivery of drugs. The aim of the present research work is to develop buccal tablets of Lercanidipine hydrochloride to reduce dosage frequency; obtain optimized and controlled therapy, better patient compliance.

MATERIAL AND METHODS

UV Spectroscopy (Analytical study):

Primary stock solution of 1.0 mg/mL lercanidipine hydrochloride was prepared by dissolving 10.0 mg of the drug in 10.0 mL of pH 6.8 phosphate bufferl. From this, 10.0 µg/mL of the drug solution was prepared by serial dilution which was scanned between the wavelengths of 200-400 nm using UV spectrophotometer (UV-1800, Shimadzu, Kyoto, Japan) to determine the wavelength of maximum absorption.

The calibration curve of drug sample was prperaed by samplepreparation of stock & standard solutions for Lercanidipine Hydrochloride: Essential stock arrangement (1 mg/ml of Lercanidipine Hydrochloride in methanol) was readied. From essential stock arrangement auxiliary stock was readied utilizing phosphate buffer pH 6.8 (Simulated Salivary Fluid) to deliver 100µg/ml. From auxiliary stock arrangement adjustment bend norms (2, 4, 6, 8, & 10 µg/ml) were readied utilizing phosphate cushion pH 6.8. The absorbance of aliquates was estimated for all adjustment bend benchmarks at 310 nm &grap was plotted between fixations versus absorbance [8].

Preformulation study:

Particle Size: Study Unadulterated Drug Particle estimate investigation was finished utilizing Optical Microscope & Malvern Instrument.

Flow properties: The drug powder was exactly weighed (M) and poured gently through a glass funnel into graduated cylinder and the volume was noted and bulk density was determined. The tapped density was determined using tapped density apparatus.

The flow properties of drug powders were characterized in terms of carr's index, hausner's ratio and angle of repose. The Carr's index ((I_C)) and Hausner's ratio (H_R) of drug powders were calculating according to following equation:

- Carr's Index (I_C) = $\rho_{Tapped} - \rho_{Bulk} / \rho_{Tapped}$
- Hausner's ratio (H_R) = $\rho_{Tapped} / \rho_{Bulk}$

The angle of repose (θ) was measured by fixed height method. This was calculated by following equation:

- Angle of repose (θ) = $\tan^{-1}$ 2 H / D

Where H is the surface area of the free standing height of the powder heap and D is diameter of heap that formed after powder flow from the glass funnel.

The drug unmilled powder exhibited good flow characteristics, whereas after milling the material showed excellent flow properties [9].

Solubility Studies:

Solubility of lercanidipine was determined in 0.1N HCl and several buffer solutions covering entire pH range of GIT i.e. 1-8. Solubility studies were carried out by placing excess amount of drug in volumetric flasks containing 10 ml of vehicle. The dispersions were continuously agitated on rotary shaker for 48 hours. After reaching equilibrium the samples were filtered through 0.45 µm membrane filter. The filtrates were suitably diluted as needed and analyzed UV spectro-photometrically for dissolved drug.

Formulation of buccal mucoadhesive tablets of Lercanidipine:

Mucoadhesive tablets were prepared by adopting a previously established method with slight modification. Direct compression technique was applied for the tablet compression, using varying proportions of different grades of polymer. All the powders in pure form were accurately weighed. Lercanidipine Hydrochloride (LEH) was then mixed with Carbopol 940. The remaining polymers Hydroxypropyl methylcellulose (HPMC) or Sodium carboxymethylcellulose (SCMC) were mixed with talc in a separate pouch. These two mixtures were then mixed for 5 min after passing through a #40 mesh sieve. Micro crystalline cellulose (MCC 200) was mixed in a separate pouch for 2 min. Then it was mixed with the previous mixture for 5 min. Finally, magnesium stearate was added and the resultant mixtures were mixed and the blend was then compressed into tablets having an average weight of 200 mg, using a single-station tablet punch (LEMT1 to LEMT8).

Table 1: Composition of various batches of mucoadhesive buccal tablets

Ingredients	LEMT1 (mg)	LEMT2 (mg)	LEMT3 (mg)	LEMT4 (mg)	LEMT5 (mg)	LEMT 6 (mg)	LEMT7 (mg)	LEMT8 (mg)
LEH	10	10	10	10	10	10	10	10
Carbopol 934	60	65	70	75	60	65	70	75
HPMC	60	55	50	45	-	-	-	-
SCMC	-	-	-	-	60	55	50	45
Magnesium stearate	10	10	10	10	10	10	10	10
MCC 200	50	50	50	50	50	50	50	50
Talc	10	10	10	10	10	10	10	10
Total weight	200	200	200	200	200	200	200	200

Evaluation of buccal mucoadhesive tablets of Lercanidipine:

Physical parameters of buccal mucoadhesive Lercanidipine Hydrochloride tablets were performed for isolation of quality of the preparation. The various parameters i.e. Appearance, thickness, weight variation, hardness, friability, drug content, mucoadhesive strength, swelling Index, in-vitro drug release study

Appearance: The prepared buccal mucoadhesive Lercanidipine Hydrochloride tablets were white yellowish color, circular shape in nature.

Thickness: Randomly selected three tablets were determined with vernier calipers. Calculate the mean thickness of the tablets.

Weight variation: Randomly selected in each formulation of twenty tablets, weighed individual tablets separately. Calculate the average mass of the tablets.

Hardness: Hardness of tablet was measured by Monsanto tester and expressed in Kg/cm2. Randomly three tablets were selected in every formulation, measure the hardness by placing each tablet in obliquely among the two plungers by applying force till the tablet divide into 2 parts and reading was noted.

Friability: This test performed to assess the capacity of the tablet to with stand wear and tear in transportation, packing. Twenty tablets are weighed and put in the plastic chamber and pivot for 4 minutes. In this revolution the tablet falls in the distance of 6 inches. The tablets are removed from the chamber and weighed.

Drug content: Randomly selected 20 tablets in every formulation. Tablets taken into motor triturate until to get fine powder. 10 mg of Lercanidipine Hydrochloride fine powder taken in 100ml volumetric flask & make up final volume with pH 6.8 phosphate buffer and subjected for filtration. Each sample measured for drug content at max 307 nm in UV-Visible spectrometer.

Disintegration test A 1000 mL beaker was filled with 900 mL of distilled water and was maintained at a temperature of 37 + 0.5 ºC. Six tablets were placed in each of the cylindrical tubes of the basket. To avoid floating of the tablets, discs were used. The time taken to break the tablets into small particles was recorded. The limit for buccal tablets is 4 hours.

Surface pH study: The surface pH must be closed to the salivary pH, so that it would not irritate the buccal mucosa. The salivary pH has the range of 6.5 to 7.5. The tablets were allowed to swell for 2 hours in 1 mL of distilled water. The surface pH of the tablet was then measured using a digital pH meter. The pH electrode was placed near the surface of the tablet and was allowed to equilibrate for 1 minute before reading the measurement.

Swelling Index: The swelling study was performed on petri dishes containing 1% agar gel. Four tablets were weighed and placed in a petri dish. The petri dishes contained 4 tablets, and each was placed in an incubator at 37 ºC + 1 ºC. [10] After 0.5, 1, 1.5, 2, 2.5, 3 hours, excess water on the surface was carefully removed using the filter paper without pressing. The tablets were reweighed and the swelling index was calculated using the formula:

$$\text{Swelling Index} = \frac{Wi \times Wf}{Wi} * 100$$

Wi Where Wi is the initial weight and Wf is the final weight of the tablet. Appropriate swelling property of buccal formulations is needed for proper adhesion

In vitro drug release studies:

In vitro drug release studies were carried out using USP II (rotating paddle) dissolution apparatus (Elecrolab TDT 08L) with minor modifications. The dissolution medium consisted of 200 ml of phosphate buffer pH 6.8 with 2.5% polysorbate 80. The release study was performed at 37°C ± 0.5°C, with a rotation speed of 25 rpm. The backing layer of the buccal tablet was attached to the glass disk with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. Samples of 5 ml were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through 0.2-µm Whatman filter paper and analyzed after appropriate dilution by UV spectrophotometer (Shimadzu, 1800) at 307 nm. The drug was quantified by UV spectrophotometry (1601 Shimadzu). All the measurements were made in triplicate and expressed as mean ± RSD. The steady-state flux was calculated from the slope of the linear region ofthe cumulative amount of Lercanidipine Hydrochloride permeated versus time plot. The absorbance of aliquates was estimated for all adjustment bend benchmarks at 307 nm [11].

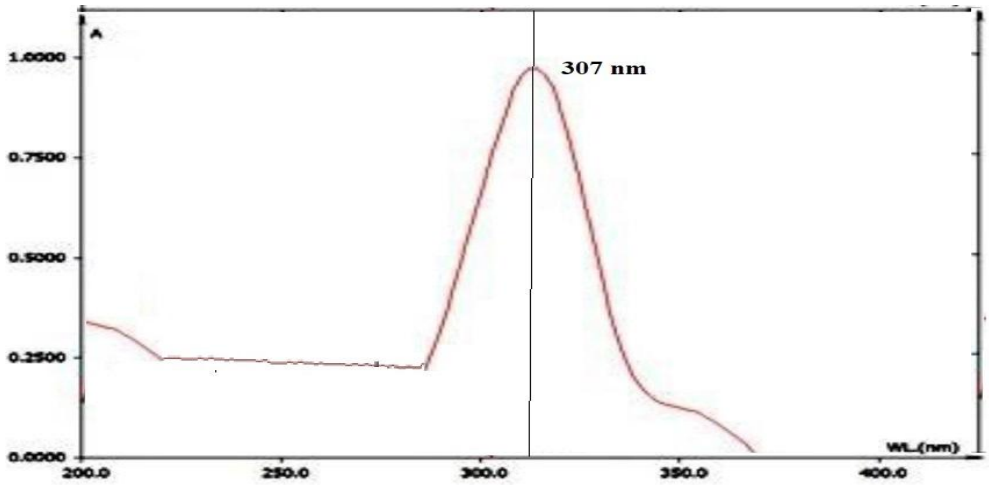

Figure 1: Determination of maximm wavelength (λmax) of Lercanidipine Hydrochloride by Using phosphate buffer pH 6.8

Table 2: Different quality control evaluation parameters of the buccal mucoadhesive granules of different batches

Formulation code	Angle of repose (θ) Mean ± SD (n=3)	Bulk density (g/cc) Mean (n=3)	Tapped density (g/cc) Mean (n=3)	Carr's index (%)	Hausner's ratio
LEMT1	27.02 ± 0.21	0.541	0.617	12.32	1.14
LEMT2	28.47 ± 0.62	0.509	0.597	14.74	1.17
LEMT3	23.11 ± 0.42	0.583	0.654	10.86	1.12
LEMT4	26.36 ± 0.09	0.546	0.628	13.06	1.15
LEMT5	23.05 ± 0.37	0.861	0.947	9.08	1.1
LEMT6	25.54 ± 0.26	0.772	0.869	11.16	1.13
LEMT7	26.68 ± 0.32	0.781	0.876	10.84	1.12
LEMT8	23.33 ± 0.17	0.954	1.046	8.79	1.1

RESULT AND DISCUSSION

Analytical study: The UV Spectroscopy of drug Lercanidipine was done and λmaxof drug was found to be 307 nm as shown in Figure 1.The standard curve of drug was plotted by concentration from 2-10 µg/ml, by checking the absorbance at 307 nm utilizing UV spectrophotometer. The linearity was watched great inside these concentrations and the linearity plot was appeared in Figure 2.

Preformulation study: Preformulation is characterized as an examination of physicochemical properties of medication substance, independently and in blend with excipients. Before beginning the manufacturing procedure of any formulation, chosen active ingredient and polymers were subjected for assessment like description, loss on drying and organoleptic properties. The obtained results were satisfactory in all preformulation studies. The unadulterated active ingredient and different excipients were stuffed in shut vials and subjected to quickened air conditions for four weeks. At that point the physical observation was done and adjusted that the active ingredient and blends does not demonstrate any adjustment in their physical properties.Lercanidipine HCl (crystalline form) is a yellow powder soluble in methanol and practically insoluble in water. Solubility of lercanidipine was determined in several reagents/buffers covering entire pH range of GI tract. Results obtained in solubility study that drug is practically insoluble in water but its solubility marginally increases in acidic pH. Above pH 5 its solubility again decreases. Thus it can be inferred that lercanidipine is practically insoluble over the entire pH range of GIT.

Characterization of tablets

Flow Properties of granules: The results of the granules evaluation suggestedthat all the granules exhibited the good flowproperties. The formulation blends were directlycompressed using 8 mm flat faced punch on tablet compress machine

Tablet thickness and tablet diameter: All the tablets are within the acceptable range for tablet thickness with values ranging from 4.71 mm to 4.80 mm. Tablet diameter of the tablets showed values ranging from 8.01 mm to 8.08 mm, which fall within the acceptable range.

Weight variation test: The specification of tablet weight with 200 mg is ±5% difference. The tablet weights should be 205 mg to 195 mg.

Hardness test: The tablet hardness shows that all tablets are within the range. The results show acceptable resistance of the tablet to shipping during storage and transport. All the tablets fall within the in-house hardness range of 4.8 kg to 5.5 kg.

Friability test: The percent friability should not be more than 0.8% for new formulations. All tablets are within range, therefore, the tablet is resistant to breaking due to storage and transportation.

Content uniformity test: The drug content varied between 97.67 to 103.03% which reflects good uniformity in drug content among different batches.

Disintegration test: All the tablets disintegrated within 60 sec.

Surface pH study: The surface pH of the tablet should be close to the salivary pH so that the tablet will not irritate the buccal mucosa. The salivary pH is 6.50 to 7.50. Since the surface pH of the buccal tablet is within the limits of salivary pH, it shows that the tablet will not irritate the buccal mucosa.

Swelling index study: The percent swelling of all formulationswere 55.90% and 54.03%, respectively. The swelling property of all the batches was performed by evaluating the swelling index at different time intervals (1, 2, 4, and 8 h). All the formulations showed an appreciable increase in swelling index, proportional to the time increased, and achieving maximum swelling effect at 8 h. The tablets did not show any significant change in their morphological shape and form, throughout the study. The highest swelling was shown by the batch LEMT8 containing CP and SCMC i.e. 450.19% whereas the lowest swelling behavior was shown by the batch LEMT1 (112.23%) containing HPMC and CP.The mucoadhesive strength of the tablet was mainly attributed to the amount of CP present. The CP and SCMC are major contributing ingredients for the swelling index, where SCMC is a more powerful swelling agent than CP. Moreover, the dissolution profile was mainly influenced by SCMC concentration. To achieve the desired characters of the mucoadhesive tablet, the proper combination of all the polymers is crucial. Among all 8 different batches, LEMT5–LEMT8 exhibited rapid drug release. Due to this reason, these batches could not meet the sustained release criteria. Also, they had a relatively higher swelling index than the normal. Thus, further modification and study of these batches is necessary to achieve desired characters (Table 3).

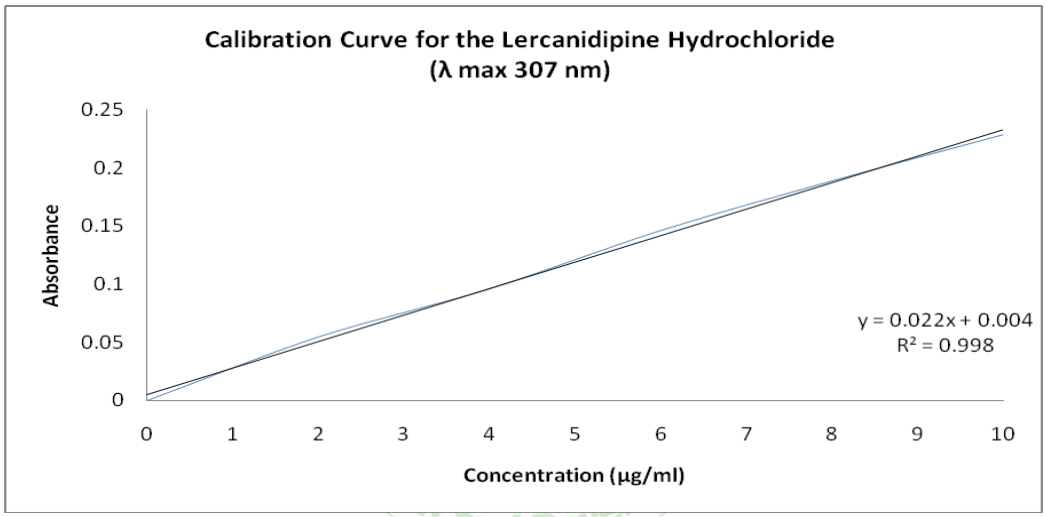

Figure 2: Calibration Curve for Lercanidipine Hydrochloride by Using phosphate buffer pH 6.8

Table 3: Different quality control evaluation parameters of the buccal mucoadhesive tablets of different batches

Formulation Code	Hardness (kg/cm2) Mean ± SD (n=3)	Thickness (mm) Mean ± SD (n=3)	Average weight (mg) Mean ± SD (n=10)	Friability (%)	Drug content (%) Mean ± SD (n=3)
LEMT1	5.87 ± 0.16	3.03 ± 0.16	206.8 ± 1.2	0.11	99.37 ± 0.82
LEMT2	5.71 ± 0.14	3.14 ± 0.14	201.7 ± 1.2	0.18	97.55± 0.84
LEMT3	5.81 ± 0.13	3.23 ± 0.13	207.6 ± 1.3	0.16	99.83 ± 1.13
LEMT4	7.01 ± 0.17	3.21 ± 0.09	208.4 ± 0.8	0.13	98.24 ± 0.87
LEMT5	6.57 ± 0.08	3.11 ± 0.08	202.8 ± 1.0	0.18	101.13 ± 0.66
LEMT6	6.02 ± 0.09	3.08 ± 0.17	206.1 ± 0.9	0.13	102.50 ± 0.72
LEMT7	6.72 ± 0.09	3.07 ± 0.09	206.9 ± 0.8	0.17	99.45 ± 1.12
LEMT8	6.81 ± 0.15	3.10 ± 0.15	209.6 ± 1.1	0.19	99.31 ± 0.76

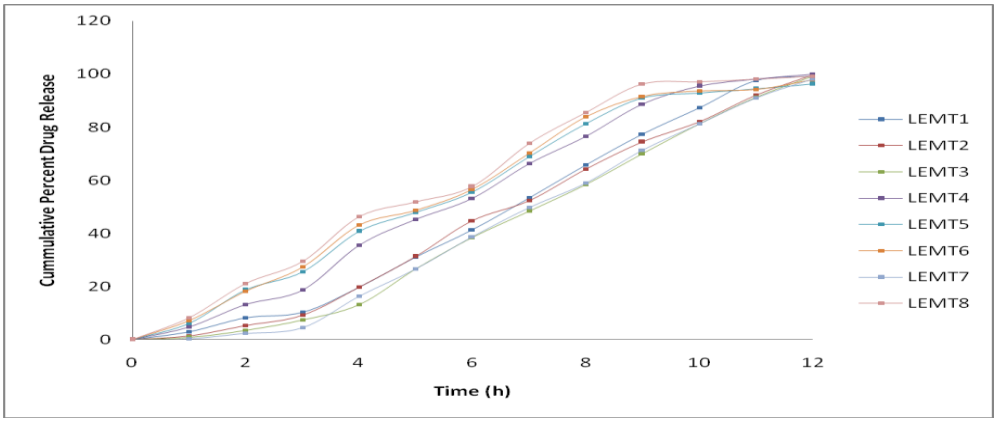

Figure 3: Zero-order kinetic plot of buccal mucoadhesive tablets of different batches

In vitro dissolution studies:

To explore the effect of polymer composition and proportion in drug release behavior, the in vitro dissolution study of formulated batches of mucoadhesive tablets was carried out. The highest and lowest drug release was observed in LEMT8 (106.14%) and LEMT3 (44.82%) respectively. In the case of batches with CP and HPMC (LEMT1–LEMT4), the drug release was found to be relatively low even after 12 h, i.e. 88.34%, 74.72%, 44.82%, and 52.82%, respectively. Similarly, the higher drug release patterns were shown by the combination of CP and SCMC (LEMT5–LEMT8), where the drug release was reported to be 104.82%, 103.5%, 103.24%, and 101.34%, respectively within 3 h. The in vitro drug release studies revealed that the release of aceclofenac depends upon the nature and proportion of polymers used. In the case of the batches containing CP and HPMC (LEMT1–LEMT4), the percentage of drug release was comparatively low even after 12 h. It has been reported that the drug release profile is decreased with increasing the proportion of HPMC. Slowly hydrating nature and comparatively low viscosity of the HPMC may lower the rate of dissolution. HPMC can facilitate a prolonged drug release, as it swells steadily to form a gel which is then dissolved in the water releasing the drugs. Similarly, the rate of drug release is inversely proportional to the amount of CP present in the formulation. When CP comes in contact with water, it swells well and its viscosity becomes very high which ultimately hinders the drug release. The lower rate of drug release in the batches LEMT3 and LEMT4 (having the highest amount of CP) also supported this statement. Also, in the case of the batches containing CP and SCMC (LEMT5– LEMT8) the percentage of drug release was very high (101.34–104.82%) even within 3 h. This can be credited to the higher extent of swelling of SCMC. This result was further proved by the swelling studies results, where the maximum swelling behavior was also shown by the batches having a high dissolution profile. Interestingly, we reported that there was a gradual decrease in dissolution rate from LEMT5 (104.82%) to LEMT8 (101.34 %), as the proportion of SCMC was gradually reduced.The batches containing CP and HPMC (LEMT1– LEMT4), showed the effective sustain release property but the drug release was ineffective in LEMT2– LEMT4. Interestingly, LEMT1 satisfied the condition of mucoadhesive strength, sustained and effective release (Figure 3). Thus this formulation was considered to be effective to meet all the criteria of mucoadhesive tablet. Moreover, this study also suggested that HPMC can play a significant role to regulate the swelling behavior, bioadhesion force, and drug release rate of the tablet. Although it has moderately swelling property, it enables steady entry and entrapment of liquid in the polymeric network, which is very significant to achieve sustained release of the drug. Thus many researchers prefer the combination of HPMC/CP mixture as a bioadhesive material.

SUMMARY AND CONCLUSION:

The study was conducted to formulate and evaluate mucoadhesive buccal tablets of lercanidipine HCl with a sustained release property, to achieve patient compliance for the management of different types of pain. Among all 8 different batches, LEMT1 showed sustained and effective drug release, swelling index as well as mucoadhesive strengths. Its physicochemical properties also complied with the pharmacopoeial standards. The results also demonstrate that CP has a major role to increase the mucoadhesive strength. The swelling behavior of the formulation can be optimized by changing the proportion of CP and SCMC. However higher concentration of SCMC can result in abrupt release of the drugs. Therefore HPMC can play a significant role to check the swelling behavior and drug release rate. However, extensive research in suitable polymers and drug candidates is indispensable. Moreover, the formulation of an aceclofenac mucoadhesive tablet can be an effective alternative route to prevent the first-pass effect and to improve the bioavailability of aceclofenac through the mucosal membrane. It can also enhance patient compliance by fascinating extended release of the drug.

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