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OPTIMIZING MUCOADHESIVE TABLETS OF LERCANIDIPINE: FORMULATION DEVELOPMENT AND EVALUATION

Vikash Singh*, Mrs. Reena Shende, Dr. Satkar Prasad
RKDF School of Pharmaceutical Sciences, Bhopal (M.P.)

Abstract:
Arterial hypertension, the prevailing cardiovascular ailment associated with escalating obesity rates and sedentary lifestyles, often necessitates changes in therapy due to the challenges posed by traditional antihypertensive medications. This study endeavors to address these issues through the development and evaluation of mucoadhesive buccal tablets of Lercanidipine. Formulation and evaluation procedures were conducted according to standard protocols, resulting in six formulations with varying ingredient concentrations. The results indicated that the bulk density of the formulations ranged from 0.374 to 0.385, while tapped density varied from 0.473 to 0.492. The compressibility index fell within the range of 21.75 to 23.00, and the Hausner ratio ranged from 1.278 to 1.299. Formulation F3 exhibited the highest drug content at 99.45±0.20%. The thickness and hardness for F3 were 3.11±0.04 mm and 5.4±0.4 kg/cm^2, respectively, while weight variation and friability were measured at 246±7 mg and 0.658±0.013%. The maximum swelling in the F3 formulation at 12 hours reached 103.25%, indicating its potential for effective drug release. The % Cumulative Drug Release for F3 at 12 hours was observed to be 99.45%. Regression coefficient values were compared, revealing that the 'r2' values of the First Order kinetics were maximized, reaching 0.978. This suggests that drug release from the formulations follows First Order kinetics. In conclusion, the F3 formulation demonstrated ideal parameters, ensuring rapid action and offering a viable alternative to traditional tablets for the management of arterial hypertension.

Keywords: *Hypertension, Buccal drug delivery, Muucoadhesive tablets, Lercanidipine*

Corresponding author:
Vikash Singh,
RKDF School of Pharmaceutical Sciences, Bhopal (M.P.)
vikassingh229206@gmail.com

QR code

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INTRODUCTION:

Hypertension stands as a leading modifiable risk factor for mortality and disability, contributing to a spectrum of cardiovascular complications, including stroke, accelerated atherosclerosis, heart failure, and chronic kidney disease. Its impact extends to the prevalence of cardiovascular events and mortality globally, with significant associations observed in various conditions such as first myocardial infarction, stroke, heart failure, and peripheral arterial disease. Additionally, hypertension plays a substantial role in diverse health issues, encompassing sudden cardiac death, dissecting aortic aneurysm, angina pectoris, left ventricular hypertrophy, thoracic and abdominal aortic aneurysms, chronic kidney disease, atrial fibrillation, diabetes, vascular dementia, and ophthalmologic complications (Chiang et al., 1969; Oliveros et al., 2020).

The primary approach to managing hypertension involves lifestyle modifications, emphasizing weight loss, dietary sodium reduction, potassium supplementation, adopting a healthy eating pattern, engaging in physical exercise, and practicing moderate alcohol consumption. Pharmacological therapy becomes necessary, and first-line remedies include thiazide or thiazide-like diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and calcium channel blockers.

Conventional dosage forms of antihypertensive medications present challenges, necessitating therapy changes and leading to negative effects such as gastrointestinal disturbances, hypotension, bradycardia, heart failure, and hepatotoxicity. In response, the development of sustained-release medications emerges as a viable solution, offering benefits such as reduced dose frequency, prolonged efficacy, increased bioavailability, and enhanced pharmaceutical safety and efficacy (Cutler et al., 2007; Ahuja et al., 1997).

The proposal of mucoadhesive drug delivery systems stems from their ability to provide rapid absorption and enhance bioavailability, facilitated by a large surface area and high blood flow. Various mucoadhesive dosage forms for oral drug delivery have been suggested, including patches, tablets, films, gels, discs, strips, and ointments. Mucoadhesion refers to the interaction between a mucin surface and a synthetic or natural polymer. It involves the capacity of synthetic or biological macromolecules to adhere to mucosal tissues.
Mucoadhesive controlled release devices offer advantages such as improved drug concentration effectiveness within the therapeutic range, prevention of drug dilution in bodily fluids, and targeted drug localization at specific sites. Additionally, mucoadhesion extends the contact duration and intimacy between a polymer-containing medication and the mucosal surface. This combined effect, involving direct drug absorption and a decrease in excretion rate due to prolonged residence time, leads to enhanced medication bioavailability, allowing for smaller doses and less frequent administration. Drugs absorbed through the mucosal lining can directly enter the bloodstream, avoiding enzymatic breakdown in the gastrointestinal tract (Kharenko et al., 2009; Macedo et al., 2020).

Buccal drug administration presents an attractive alternative to oral delivery, addressing drawbacks associated with the latter, such as first-pass metabolism and drug degradation in the gastrointestinal environment. Moreover, the oral cavity's accessibility makes buccal medication delivery particularly well-suited for self-treatment. Benefits of buccal drug administration include painless drug administration and simple withdrawal of the drug (Verma et al., 2011).

Lercanidipine, a dihydropyridine calcium-channel blocker, finds application in treating hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina, either alone or in combination with an angiotensin-converting enzyme inhibitor. Lercanidipine operates by reducing extracellular calcium influx across cardiac and vascular smooth muscle cell membranes. This leads to various cardiovascular effects, including coronary and systemic artery dilation, increased oxygen delivery to myocardial tissue, reduced total peripheral resistance, decreased systemic blood pressure, and lowered afterload (Bang et al., 2003). Considering the attributes of buccal mucoadhesive drug delivery systems, this study aims to develop and evaluate mucoadhesive buccal tablets of Lercanidipine.

MATERIALS & METHODS:

Procurement of drug

Lercanidipine was obtained from bioplus life science banglore.

Chemicals

Methanol, Ethanol, Chloroform, Hydrochloric acid (HCl), KH_2PO_4, NaOH, HPMC K-4, Carbopol, Na Alginate, Citric acid, Talc, Lactose, Magnesium stearate were obtained from S.D. Fine Pvt. Ltd. Mumbai & Loba Chemie Pvt Ltd, Mumbai.

Method for preparation of Lercanidipine buccal tablet

Select appropriate mucoadhesive polymers based on their compatibility with the drug and their mucoadhesive properties. Determine the optimal ratio of drug to polymers and other excipients for each formulation (F1 to F6). Weigh the specified amounts of Lercanidipine, mucoadhesive polymers, and other excipients according to the formulation for each batch.Thoroughly mix the weighed ingredients in a suitable blending apparatus to achieve a homogenous blend.Ensure uniform distribution of the drug and excipients to enhance the tablet's overall quality.

Employ a direct compression method to compress the blended powder into tablets. Utilize a tablet compression machine, adjusting parameters such as compression force and dwell time according to the specific requirements.

Table 1: Various formulations of buccal tablets of Lercanidipine

Ingradient (mg)	F1	F2	F3	F4	F5	F6
Lercanidipine	10	10	10	10	10	10
HPMC K-4	25	50	75	25	50	75
Carbopol	-	-	-	25	50	75
Na Alginate	25	25	25	25	25	25
Magnesium stearate	10	10	10	10	10	10
Talc	10	10	10	10	10	10
Lactose	150	125	100	125	75	25
Total Weight	250	250	250	250	250	250

Evaluation of Tablets

The tablets underwent comprehensive evaluation based on various parameters to ensure their quality and performance. The assessments included:

General Appearance:

Five tablets from different batches were randomly selected for visual inspection. Organoleptic properties such as color, odor, taste, and shape were assessed. Ratings were assigned: Very good (+++), good (++), fair (+), poor (-), very poor (- -) (Fatima et al., 2015).

Thickness and Diameter:

Vernier calipers were used to measure the thickness and diameter of five tablets from each batch. Average values were calculated for each parameter.

Drug Content:

Twenty tablets were selected, and the amount of drug in each tablet was determined. The tablets were crushed, and an equivalent of 10 mg of the drug was dissolved and analyzed spectrophotometrically at 234 nm.

Hardness:

The hardness of five tablets from each formulation was measured using the Monsanto hardness tester (Cadmach).

Friability:

Friability was determined using a Friability tester (Electro Lab) with ten tablets. Tablets were rotated, dedusted, and reweighed to calculate the percentage of weight loss.

Uniformity of Weight:

Twenty tablets were randomly selected from each batch, individually weighed, and the average weight and standard deviation were calculated.

Swelling Index:

Swelling studies were conducted using USP type 1 Dissolution Test Apparatus. Percent hydration (swelling index) was calculated at different time intervals using the formula: Swelling index = (W2 - W1) × 100/W2.

Dissolution Rate Studies:

In vitro drug release was assessed using USP type II dissolution apparatus. Dissolution was conducted in phosphate buffer pH 6.8 for 12 hours, with samples withdrawn at specified intervals.

Mathematical Treatment of Release Data:
The quantitative analysis of dissolution results was performed using mathematical formulas expressing dissolution as a function of measurement attributes.

RESULTS & DISCUSSION:

The bulk density, tapped density, compressibility index, and Hausner ratio ranged within specific values for the six formulations. F3 exhibited the highest drug content (99.45±0.20%), optimal thickness (3.11±0.04 mm), and hardness (5.4±0.4 kg/cm2). Weight variation and friability were within acceptable limits for F3 (246±7 mg and 0.658±0.013%, respectively).

Formulation F3 demonstrated the highest swelling index (103.25%) after 12 hours, indicating superior water absorption and swelling capacity, potentially leading to enhanced drug release properties. Comparatively lower swelling indices were observed for F2 and F4, which might impact their drug release behavior.

Tablets containing polymers with stronger swelling characteristics exhibited maximum drug release rates. The % Cumulative Drug Release for F3 at 12 hrs was 99.45, and First Order kinetics best described the drug release from formulations (r2 = 0.978).

The optimized formulation, F3, displayed favorable characteristics and performance in various parameters, suggesting that the incorporation of natural gums contributed to the desired qualities of the buccal tablets. Further investigations and correlation with in vivo studies are recommended for a comprehensive evaluation of the formulations' efficacy.

Table 2: Result of pre-compression properties of Lercanidipine

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.385	0.492	21.75	1.278
F2	0.375	0.487	23.00	1.299
F3	0.382	0.491	22.20	1.285
F4	0.369	0.473	21.99	1.282
F5	0.374	0.483	22.57	1.291
F6	0.378	0.489	22.70	1.294

Table 3: Results of post compression properties buccal tablets

Formulation code	Thickness (mm)	Hardness (kg/cm2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3
F1	3.05±0.05	5.1±0.2	255±5	0.658±0.012	98.12±0.32
F2	3.08±0.03	5.2±0.3	248±6	0.745±0.025	98.78±0.14
F3	3.11±0.04	5.4±0.4	246±7	0.658±0.013	99.45±0.20
F4	3.07±0.05	5.1±0.3	247±8	0.741±0.011	97.85±0.16
F5	3.08±0.03	5.3±0.2	252±5	0.882±0.015	98.36±0.17
F6	3.06±0.02	5.2±0.3	250±6	0.798±0.015	98.05±0.11

Table 4: Results of % Swelling Index of Lercanidipine buccal tablets

Formulation Code	% Swelling Index			
	2 hrs.	4 hrs.	8hrs.	12hrs.
F1	26.58	55.65	73.32	89.98
F2	30.25	48.85	72.23	83.32
F3	35.65	59.98	89.98	103.25
F4	25.65	63.32	79.98	86.65
F5	35.65	68.85	82.23	98.85
F6	36.65	65.58	75.65	96.65

Table 5: *In-vitro* drug release study of buccal tablets

Time	% Cumulative Drug Release					
(hr)	F1	F2	F3	F4	F5	F6
0.5	36.65	30.45	22.23	19.98	18.85	16.65
1	59.98	45.65	31.14	28.85	25.65	22.12
1.5	63.32	55.65	45.65	39.98	35.45	30.56
2	78.85	68.85	58.98	53.32	50.21	45.65
3	89.98	73.32	67.74	63.32	59.98	52.23
4	98.85	88.95	78.85	74.45	68.85	63.32
6	-	98.85	89.98	82.23	73.32	72.25
8	-	-	93.32	89.98	82.23	78.85
12	-	-	99.45	93.32	88.98	87.65

Table 6: *In-vitro* drug release data for optimized formulation F3

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	22.23	1.347	77.77	1.891
1	1.000	0.000	31.14	1.493	68.86	1.838
1.5	1.225	0.176	45.65	1.659	54.35	1.735
2	1.414	0.301	58.98	1.771	41.02	1.613
3	1.732	0.477	67.74	1.831	32.26	1.509
4	2.000	0.602	78.85	1.897	21.15	1.325
6	2.449	0.778	89.98	1.954	10.02	1.001
8	2.828	0.903	93.32	1.970	6.68	0.825
12	3.464	1.079	99.45	1.998	0.55	-0.260

Table 7: Regression analysis data of Lercanidipine buccal tablets

Batch	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
	r^2	r^2	r^2	r^2
F3	0.776	0.978	0.909	0.940

CONCLUSION:

Mucoadhesive buccal tablets containing carbopol 934, HPMC K4M, and sodium alginate as mucoadhesive polymers were formulated in six different preparations. All formulations exhibited favorable characteristics in terms of bulk density, tapped density, Hausner's ratio, and Carr's index, meeting standard limits. Post-compression evaluations, including thickness, weight variation, hardness, friability, drug content, and surface pH, adhered to official standards.

In vitro studies, encompassing swelling, mucoadhesive strength, and drug release, revealed that all formulations complied with established limits. Notably, formulation F3 demonstrated significant swelling properties and an optimal release profile. Therefore, it can be inferred that F3 holds promise for buccal administration, particularly for anti-hypertensive drug delivery.

The use of mucoadhesive buccal tablets for Lercanidipine presents a strategic approach to bypass extensive hepatic first-pass metabolism, potentially improving bioavailability. The study's results suggest that Lercanidipine is amenable to the development of mucoadhesive buccal tablets. However, further exploration through clinical trials and commercial exploitation is warranted to ascertain its effectiveness and practical utility in therapeutic treatment.

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