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FORMULATION, DEVELOPMENT AND EVALUATION OF MUCOADHESIVE TABLETS OF LERCANIDIPINE

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ABSTRACT

Arterial hypertension is the most common cardiovascular disease today & is linked to rising obesity rates and sedentary lifestyles. The traditional dosage form of antihypertensive medicines causes a lot of trouble and changes in therapy, as well as various Because mucoadhesive drug delivery provides rapid absorption and good bioavailability negative effects this study aims at development & evaluation of mucoadhesive buccal tablets of Lercanidipine. The formulation & evaluation of tablets was carried out as per standard protocol. Total six formulations were made by modulating the concentration of ingredients. Results revealed that the bulk density for six formulations was found to be ranged from 0.374 to 0.385. Tapped density varied from 0.473 to 0.492. Further the Compressibility index was seen to ranged from 21.75 to 23.00. The Hausner ratio was observed to be ranged from 1.278 to 1.299. The drug content was found to be maximum in F3 which is 99.45±0.20%. The thickness & hardness for F3 was noticed to be 3.11±0.04mm & 5.4±0.4 kg/cm2. While the weight variation & friability was estimated to be 246±7 mg & 0.658±0.013%. The maximum swelling in F3 formulation at 12 hours was noticed to be 103.25%. The % Cumulative Drug Release for F3 at 12 hrs was observed to be 99.45. When the regression coefficient values of were compared, it was observed that 'r2' values of First Order was maximum i.e. 0.978 hence indicating drug release from formulations was found to follow First Order kinetics. Thus, it can concluded that F3 formulation is have all ideal parameters and effective for speedy action, and appears to offer an alternative to the traditional table.

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

INTRODUCTION

The most common modifiable risk factor for death and disability is hypertension, which includes stroke, accelerated coronary and systemic atherosclerosis, heart failure, chronic kidney disease, lowering blood pressure with antihypertensive drugs, and reducing target organ damage and the prevalence of the occurrence of cardiovascular disease.

Hypertension is the leading modifiable and important risk factor for CV events and mortality in adults worldwide. Hypertension is present in 69% of adults who have their first MI, 77% of people who have their first stroke, 74% of adults who have HF, and 60% of older individuals who have PAD. Hypertension is also a substantial risk factor for SCD, a dissecting aortic aneurysm, angina pectoris, LVH, thoracic and abdominal aortic

aneurysms, CKD, atrial fibrillation, diabetes, vascular dementia, and ophthalmologic complications (Chiang *et al*., 1969; Oliveros *et al*., 2020).

The first-line therapy for hypertension is lifestyle change, which includes weight loss, dietary sodium reduction, potassium supplementation, a healthy eating pattern, physical exercise, and moderate alcohol consumption. Thiazide or thiazidelike diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and calcium channel blockers are first-line remedies when pharmacological therapy is required (Jackson and Bellamy, 2015; Ram, 2002).

The traditional dosage form of antihypertensive medicines causes a lot of trouble and changes in therapy, as well as various negative effects such as gastrointestinal disturbances, hypotension, bradycardia, heart failure, and hepatotoxicity. Thus, developing sustained-release medication is a viable option for reducing dose frequency, achieving a longer effect with increased bioavailability, and increasing pharmaceutical safety and efficacy (Cutler *et al*., 2007; Ahuja *et al*., 1997).

Because mucoadhesive drug delivery provides rapid absorption and good bioavailability due to its large surface area and high blood flow, mucoadhesive dosage forms for oral drug delivery were proposed, which include patches, tablets, films, gels, discs, strips, and ointment.Mucoadhesion is described as the interaction of a mucin surface with a synthetic or natural polymer. Mucoadhesion is also defined as the ability of synthetic or biological macromolecules to attach to mucosal tissues. Mucoadhesive controlled release devices can improve drug concentration effectiveness between the minimum effective concentration and the maximum safe concentration. They also prevent drug dilution in bodily fluids and allow for drug targeting and localization at specific sites. Mucoadhesive also increases the intimacy and length of contact between a polymer-containing medication and the mucosal surface. The combined effect of direct drug absorption and a decrease in excretion rate (due to prolonged residence time) results in enhanced medication bioavailability with smaller doses and less frequent administration. Drugs that are absorbed through the mucosal lining of tissues can enter the bloodstream directly, preventing enzymatic breakdown in the GI tract (Kharenko *et al*., 2009; Macedo *et al*., 2020).

Buccal drug administration is an appealing option to oral drug administration, particularly in terms of resolving shortcomings associated with the latter mode of dosage. By giving the medicine via buccal route, problems such as first pass metabolism and drug degradation in the GIT environment can be avoided. Furthermore, the oral cavity is easily accessible for self-treatment. The following are some of the benefits of buccal medication delivery: Drug administration is painless, and drug withdrawal is simple (Verma *et al*., 2011).

Lercanidipine, a dihydropyridine calcium-channel blocker, is used to treat hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina alone or in combination with an angiotensin-converting enzyme inhibitor. Lercanidipine decreases extracellular calcium influx across cardiac and vascular smooth muscle cell membranes.

Reduced intracellular calcium inhibits the contractile processes of myocardial smooth muscle cells, resulting in coronary and systemic artery dilation, increased oxygen delivery to myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload (Bang *et al*., 2003). Considering features of buccal mucoadhesive drug delivery system this study aims at development & evaluation of mucoadhesive buccal tablets of Lercanidipine.

MATERIALS AND METHODS

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

Direct compression was taken after to manufacture the buccal tablets of Lercanidipine[83-84]. Six different formulations (F1, F2, F3, F4, F5, and F6) were set up by direct compression. Every one of the polymers chose, drug and excipients were gone through strainer no. 40 preceding utilizing into plan. The sum and proportion of drug and polymers were weighed according

Evaluation of tablets

All the tablets were evaluated for following various parameters which includes;

General Appearance

Five tablets from various batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -) (Fatima et al., 2015).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 10ml standard flask. The powder was dissolved in 5 ml of phosphate buffer pH 6.8 and made up to volume with of phosphate buffer pH 6.8. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at λ_{max} of 234nm using of phosphate buffer pH 6.8 as blank.

Hardness

For each formulation the hardness of five tablets was resolved utilizing the Monsanto hardness tester (Cadmach).

Friability

The friability of sample of 10 tablets was estimated utilizing a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

Swelling Index

Swelling study of individual polymers and combinations was carried out using eight-stage USP type 1 (basket) Dissolution Test Apparatus (Lab India, DS 8000) at 50 rpm, and phosphate buffer pH 6.8 was used as medium, and the temperature was maintained at 37 ± 0.5°C. Weight of individual tablet was taken prior to the swelling study (W_1). The tablet was kept in a basket. The weight of tablet was taken at time interval of 2, 4, 8, 12 hours (W_2). Percent hydration (swelling index) was calculated as shown in Table 7.7 using the following formula:

Swelling index = $(W_2 - W_1) \times 100/W_2$,

Where W_1 is the initial weight of tablet and W_2 is the weight of hydrated tablet.

Dissolution rate studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml phosphate buffer pH 6.8 was set into the dissolution flask maintaining the temperature of 37 ± 0.5^0C and rpm of 75. One Lercanidipine tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 12 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 2 hours using 10ml pipette. The new disintegration medium (37^0C) was supplanted each time with a similar amount of the sample and takes the absorbance at 234 nm using spectroscopy (Reddy and Reddy, 2015).

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

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/cm^2) 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

RESULTS AND DISCUSSION

The bulk density for six formulations was found to be ranged from 0.374 to 0.385. Tapped density varied from 0.473 to 0.492. Further the Compressibility index was seen to ranged from 21.75 to 23.00. The Hausner ratio was observed to be ranged from 1.278 to 1.299. The drug content was found to be maximum in F3 which is 99.45±0.20%. The thickness & hardness for F3 was noticed to be 3.11±0.04mm & 5.4±0.4 kg/cm^2. While the weight variation & friability was estimated to be 246±7 mg & 0.658±0.013%.

Formulation F3 stands out as having the highest swelling index (103.25%) among all formulations after 12 hours. This suggests that F3 has the highest water absorption and swelling ability, potentially leading to better drug release properties. On the other hand, formulations F2 and F4 have relatively lower swelling indices, which may impact their drug release behavior.the percentage swelling index data can aid in formulating buccal tablets with optimized drug release profiles and improved therapeutic outcomes for Lercanidipine delivery. Further investigation and correlation with drug release profiles and in vivo studies would be beneficial for a comprehensive evaluation of the formulations' performance.

Tablets containing polymers with stronger swelling characteristics clearly demonstrated the maximum rate and extent of drug release. The sluggish releasemay be attributable to the gel's composition of tightly packed swelling particles.

With an increase in polymer quantity, thicker gel forms that restrict water penetration more strongly, resulting in a considerable fall in release values indicating slower medication release. The % Cumulative Drug Release for F3 at 12 hrs was observed to be 99.45. When the regression coefficient values of were compared, it was observed that ‘r2’ values of First Order was maximum i.e. 0.978 hence indicating drug release from formulations was found to follow First Order kinetics.

The optimized formulation, F3, demonstrated satisfactory results in terms of various parameters evaluated, including physical characterization, post-compression properties, % swelling index, and in vitro drug release. These findings suggest that the incorporation of natural gums in the formulation contributed to the desired characteristics and performance of the buccal tablets.

CONCLUSION

The Mucoadhesive buccal tablets were prepared using carbopol 934, HPMC K4M, sodium alginate as mucoadhesive polymer. A total of six formulations were prepared. The bulk density, tapped density; Hausner’s ratio and Carr’s index of all the formulations were found to be within the standard limits. All the post-compression characteristics of the formulations like thickness, weight variation, hardness, friability, drug content and surface pH, *in-vitro* studies like swelling, mucoadhesive strength and drug release were found to be well within the limits of official standards. Among the 6 formulations, the formulation F 3 exhibited significant swelling properties with optimum release profile. Hence it can be concluded that the formulation F 3 will be useful for buccal administration for the treatment of anti-hypertensive drug.

Hence the mucoadhesive buccal tablets of Lercanidipine may be a good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability through. From these results it was concluded that, the Lercanidipine is suitable to develop in to Mucoadhesive buccal tablets, further clinical trials and commercial exploitation is needed for the better usefulness in the intended therapeutic treatment.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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