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Controlled Release Lercanidipine Tablets: A Study on Formulation and Evaluation by Wet Granulation

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Abstract

Lercanidipine blocks the entry of extracellular calcium into vascular and cardiac muscle cells, preventing myocardial smooth muscle contraction due to decreased intracellular calcium. This results in the dilation of coronary and systemic arteries, reducing blood pressure. This study aimed to develop and evaluate lercanidipine controlled-release tablets for oral administration using polymers like HPMC K 100M, sodium alginate, and guar gum. Lercanidipine, polymers, and diluents were sieved and mixed for 10 minutes. Granules were formed using isopropyl alcohol, dried at 60°C for one hour, and sieved. The granules were lubricated with colloidal silicon dioxide (Aerosil-200) and magnesium stearate, blended for 5 minutes, and compressed using a rotary machine (average weight: 500 mg; hardness: 5-6 kg/cm^2). Bulk and tapped densities were nearly identical for all formulations. Compressibility index and Hausner ratio ranged from ≤18 to 1.09-1.21, indicating good flow properties. Tablet thickness ranged from 5.82 to 5.91 mm, hardness from 5.9 to 6.3 kg/cm^2, and friability was less than 1.0 %W/W. Drug content was between 98-102%. The controlled-release order from dissolution data was F9 > F7 > F8, showing optimal release with a combination of HPMC and two natural polymers.

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INTRODUCTION

The idealized objective emphasizes the significance of the drug's location and the timing of administration. Unlike temporal delivery, which regulates how quickly a medicine reaches its target, spatial placement refers to conveying a drug to a particular organ or tissue. The creation of a more reliable technique of sustained drug release might address both concerns. While much research has concentrated on oral dose forms that

deal with the time component of pharmaceutical administration, many innovative techniques now being explored may also deal with the space component [1]. Some frequent drug delivery systems include: "solutions, suspensions, capsules, tablets, emulsions, aerosols, foams, ointments, and suppositories." For this discussion, you can think of these dosage forms as immediately releasing their active ingredients into an absorption pool. This is shown simply in the following kinetic scheme: "Kr, Ka, and Ke" are first-order rate constants for drug release, absorption, and total elimination, respectively; the absorption pool is the solution of the drug at the site of absorption. If the medication is immediately released from a typical dose form, the rate-limiting phase is the drug's passage across a biological membrane, such as the intestinal epithelium [2].

MATERIALS AND METHODS

MATERIALS

Lercanidipine is an API, and other polymer mixtures such as HPMC K100M, Sodium Alginate, Guar gum, and Avicel PH 102 are intragranular, whereas Aerosil and Mag.Stearate are extragranular.

METHODS

Preparation of matrix tablets by non-aqueous wet granulation method:

1. Lercanidipine+ polymers+ Diluent are shifted through sieve no. 60# and blended in a poly bag for 10 min.
2. The above blend was granulated with isopropyl alcohol. The granules were dried in a hot air oven at 60°C for 1 hr.
3. The dried granules were passed through # 30
4. The above granules were lubricated with sieve no. 60#. Sifted colloidal silicon dioxide (Aerosil-200) and magnesium stearate were blended in a poly bag for 5 min.

Table 1 Lercanidipine CR formulation tablet for F1 –F6 formulations

S. No	Ingredients	F1 30% HPMC	F2 45 % HPMC	F3 30% G.G.	F4 45 % G.G.	F5 30% S.A.	F6 45% S.A.
Intragranular							
	Lercanidipine	10	10	10	10	10	10
	HPMC K100M	15	30	--	--	--	--
	Sodium Alginate	--	--	--	--	15	30
	Guar gum	--	--	15	30	--	--
	Avicel PH 102	170	155	170	155	170	155
Extra granular							
	Aerosil	2.5	2.5	2.5	2.5	2.5	2.5
	Mag. Stearate	2.5	2.5	2.5	2.5	2.5	2.5
	Tablet Wt.	200.0	200.0	200.0	200.0	200.0	200.0

Table 2 Lercanidipine CR formulation table for F7 – F9 formulations

S.No	Ingredients	Qty per Tablet (mg)			Purpose
		F7 HPMC+SA	F8 HPMC+GG	F9 HPMC+SA+GG	
Intragranular					
1	Lercanidipine	10	10	10	API
2	HPMC K100M	30	30	30	Synthetic C.R. Polymer
3	Sodium Alginate	50	--	25	Natural C.R. Polymer
4	Guar gum	--	50	25	Natural C.R. Polymer
5	Avicel PH 102	105	105	105	diluent
Extra granular					
6	Aerosil	2.5	2.5	2.5	Glidant
7.	Mag. stearate	2.50	2.50	2.50	lubricant
	Tab Wt.	200	200	200	

5. Lubricated granules were compressed by the rotary machine having round concave-shaped punches with an average wt. of 500 mg & min hardness of 5-6 kg/cm^2.

Parameters for evaluation

Pre Compression Parameters [3] - [5]

Angle of repose: Angle of repose is defined as the maximum angle between the surface of the pile of powder and the horizontal plane. A fixed funnel method was used. A funnel was fixed with its tip at a given height (h) above a flat horizontal surface on which graph paper was placed. The powder was carefully poured through the funnel until the apex of the conical pile formed just reached the tip of the funnel. These studies were carried out before and after incorporating lubricant/glidant. The angle of repose (ɵ) was then calculated.

$$\theta = \tan^{-1}(h/r)$$

Bulk density: Bulk density was determined using bulk density apparatus; during measurement, accurately weighed quantities of the powder were taken in a measuring cylinder, and the volume and weight of the total powder were. Bulk density is expressed in gm/ml and is given by,

$$BD = W/V_o$$

Tapped density: Tapped density was determined using the Tapped density apparatus. During measurement, an accurately weighed quantity of the powder was taken in a measuring cylinder, and the volume of powder after 30 tappings and the weight of the total powder.

$$TD = W/V_F$$

Compressibility index (or) Carr's index: The compressibility index is an important measure obtained from the bulk and tap densities. A material with values less than 20 to 30% is defined as a free-flowing material; based on the apparent bulk density and tapped density, the percentage compressibility of the bulk drug was determined using the following formula.

$$\text{Compressibility index} = \frac{(\text{T. D.} - \text{B. D.})}{\text{TD}} \times 100$$

Hausner's ratio: It indicates the flow properties of the powder. The ratio of tapped density to bulk density of the powder is called Hausner's ratio.

Post Compression Parameters [6-9]

Average Weight: The weight of the Tablet being made was determined to ensure that a tablet contains the proper amount of the drug. Twenty tablets were selected randomly from each Formulation and weighed on an electronic weighing balance. The average weight of the tablets was determined. The weight of individual tablets was compared with the average weight variation.

Thickness: Thickness was measured using a calibrated vernier caliper. It was determined to check the thickness of the Tablet. Five tablets of each Formulation were picked randomly, and thickness was measured individually.

Hardness: The hardness of ten tablets was measured using a Monsanto tester. Resistance of the Tablet during transportation or breakage under storage conditions and handling before usage depends on its hardness. The hardness was measured in terms of kg/cm^2. Five tablets were chosen randomly and tested for hardness. The average hardness of five tablets was recorded.

Friability: The friability of the prepared tablets was determined using the Roche friability apparatus. It is expressed in percentage (%). To calculate the percentage of friability, determine the initial weight of ten tablets and transfer it into friability. The friability was operated at 25 rpm for four minutes. After four minutes, the tablets were weighed again. The % friability was then calculated using a formula.

$$\%\ \text{Friability} = \frac{\text{initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

Drug content uniformity: The drug content of prepared tablets was accurately weighed and finely powered by a pestle in a mortar. A weighed Tablet of each powder equivalent to 400mg of Clindamycin Hydrochloride was transferred in a volumetric flask, dissolved in 60ml of 0.1N HCL, and the content of the flask was sonicated for 15 minutes. Then, the volume was made up to 100ml. The samples were analyzed using a UV-visible spectrophotometer, and the drug concentration in the sample was calculated.

***In-vitro* dissolution studies [10]:** Dissolution of the tablets was carried out on USP XXXIII dissolution type II apparatus using a paddle. The

Tablet was fixed to the paddle by hydration mechanism 900 ml of 0.1N HCL as dissolution medium was filled in a dissolution vessel, and the temperature of the medium was set at 37± 0.5°c. The rotational speed of the paddle was set at 100 rpm. At particular intervals, 5 ml of sample was withdrawn at predetermined intervals of 2hr, 4hr, 6hr, 8hr, 10hr up to 12 hr, and the same volume of fresh medium was replaced. The withdrawn samples were diluted to 10 ml with 0.1N HCL, filtered, and analyzed on a U.V. spectrophotometer. The percentage of cumulative drug release was calculated [Table 5].

Data analysis [11-12]: To analyze the mechanism of release and release rate Zero order, first order, Higuchi matrix, and Peppa's model. Based on the r-value, the best-fit model was selected [Table 6].

Zero-order kinetics: Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained, can be represented by the following equation.

$$Qt = Q_o + K_o t$$

First order kinetics

The release rate data were fitted to the following equation to study the first-order release rate kinetics.

$$\text{Log } Qt = \text{Log } Q_o K_1 t/2.303$$

Higuchi's model

Higuchi developed several theoretical models to study the release of water-soluble and low-soluble drugs incorporated in semisolids and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as diffusion media. The equation is,

$$Mt/M\infty = KH\ t1/2$$

Korsmeyer- Peppas Model:

The power law describes the fractional drug release as exponentially related to the release time and adequately describes the release of drug from slabs, cylinders, and spheres, as expressed in the following equation.

$$Mt / M\infty = Ktn$$

$$\text{Log } (Mt / M\infty) = \log K + n \log t$$

Table 3 Lercanidipine CR tablets(*n=3)

F.Code	AR(°)	B.D. (g/cc.)	TD (g/cc.)	CI (%)	HR
F-1	22.170±0.15	0.5150±0.015	0.5220±0.008	13.150±1.04	1.100±0.07
F-2	31.110±0.11	0.4710±0.011	0.4760±0.012	16.230±0.23	1.210±0.11
F-3	25.710±0.13	0.5050±0.005	0.5270±0.015	14.260±0.65	1.150±0.31
F-4	23.310±0.13	0.5220±0.023	0.5190±0.022	12.360±0.26	1.090±0.23
F-5	31.110±0.11	0.4710±0.011	0.4760±0.012	16.230±0.23	1.210±0.11
F-6	25.710±0.13	0.5050±0.005	0.5270±0.015	14.260±0.65	1.150±0.31
F-7	23.310±0.13	0.5220±0.023	0.5190±0.022	12.360±0.26	1.090±0.23
F-8	31.110±0.11	0.4710±0.011	0.4760±0.012	16.230±0.23	1.210±0.11
F-9	31.110±0.11	0.4710±0.011	0.4760±0.012	16.230±0.23	1.210±0.11

Table 4 Lercanidipine C.R. tablets

F. Code	Average weight (mg) (n=20)	Thickness (mm) (n=3)	Hardness (kp) (n=3)	% Friability	%Drug Content (n=3)
F-1	500.4±0.60	5.820±0.34	5.90±0.26	0.590	99.980±0.18
F-2	502.2±0.40	5.910±0.23	6.20±0.25	0.680	100.210±0.20
F-3	499.6±0.40	5.840±0.1	6.30±0.21	0.580	99.670±0.12
F-4	498.0±0.30	5.880±0.1	5.90±0.23	0.590	100.320±0.14
F-5	499.6±0.40	5.840±0.1	6.30±0.21	0.580	99.670±0.12
F-6	502.2±0.40	5.910±0.23	6.20±0.25	0.680	100.210±0.20
F-7	500.4±0.60	5.820±0.34	5.90±0.26	0.590	99.980±0.18
F-8	502.2±0.40	5.910±0.23	6.20±0.25	0.680	100.210±0.20
F-9	499.6±0.40	5.840±0.1	6.30±0.21	0.580	99.670±0.12

Table 5 Dissolution profile

Time (hr)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
	30% HPMC	45 % HPMC	30% GG	45 % GG	30% SA	45% SA	HPMC+SA	HPMC+GG	HPMC+SA+GG
0	0	0	0	0	0	0	0	0	0
1	29.52	24.6	38.32	32.52	35.5	30.32	16.54	17.38	9.52
2	43.51	28.9	52.25	48.57	45.32	42.54	25.28	27.38	25.6
4	67.32	40.32	78.35	72.32	69.55	64.54	34.24	36.57	38.52
6	84.54	65	91.32	89.54	89.32	87.24	58.58	51.22	50.32
8	92.32	87.32	96.55	95.32	96.47	93.23	78.32	82.34	62.58
10	99.54	94.45	99.21	98.34	99.54	99.21	88.54	92.35	81.35
12	99.54	98.34	99.21	98.34	99.54	99.21	99.58	99.32	99.35

Table 6 In-Vitro Dissolution Results

Formulation code	R^2				
	Zero-order	First order	Higuchi Plot	Peppas Plot	n-Value
F1	0.929	0.961	0.990	0.980	0.513
F2	0.977	0.965	0.979	0.948	0.624
F3	0.880	0.990	0.974	0.958	0.404
F4	0.901	0.991	0.981	0.963	0.464
F5	0.911	0.980	0.984	0.97	0.455
F6	0.928	0.976	0.988	0.977	0.511
F7	0.991	0.872	0.973	0.976	0.750
F8	0.987	0.909	0.967	0.969	0.723
F9	0.994	0.829	0.969	0.976	0.869

RESULTS AND DISCUSSION

Pre-Compression studies:

Inference:

The flow characteristics of the Lercanidipine C.R. tablets were examined; Compression tablet combinations and their outcomes are shown in Table 3. The tapped density was also discovered to be comparable to the bulk density. There was sufficient flow and compressibility in the blends11, as measured by Carr's index (in the range of 16) and Hausner's ratio (1.10 to 1.21). All formulas showed satisfactory flow, with angles of repose between 22.17 and 31.11 degrees (incorporating Glidant will enhance its flow).

Inference:

The variance in weight was within the acceptable range. The thickness of tablets ranged between 5.82 and 5.91 millimeters. The hardness ranged between 5.9 and 6.2kg/cm2 for several formulations, showing good mechanical strength. The friability was 1.0% W/W for all formulations, indicating the mechanical solid resilience of the Tablet. The drug content was determined to be between 99 and 100% of the labeled amount (Table 4).

At each time point, 5 ml of sample was taken and replaced with pH 6.8 sodium phosphate buffer warmed to 37±0.5 °C

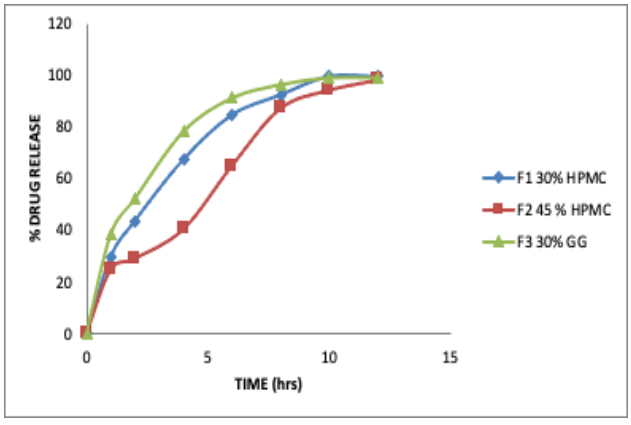

Figure 1 Zero order of F-1, F-2 and F-3 formulations of Lercanidipine

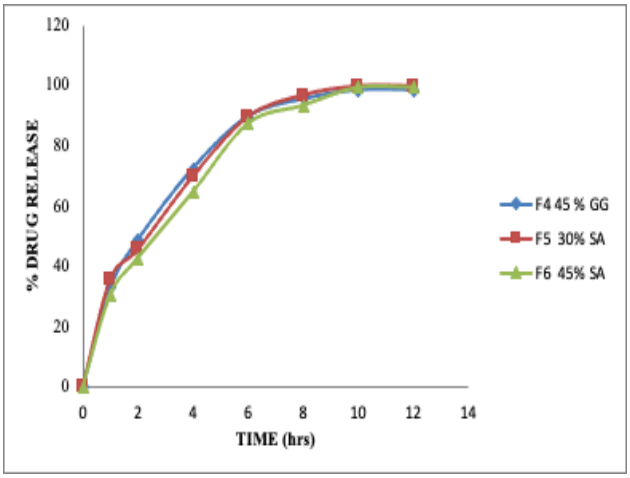

Figure 2 Zero order of F-4, F-5 and F-6 formulations of Lercanidipine

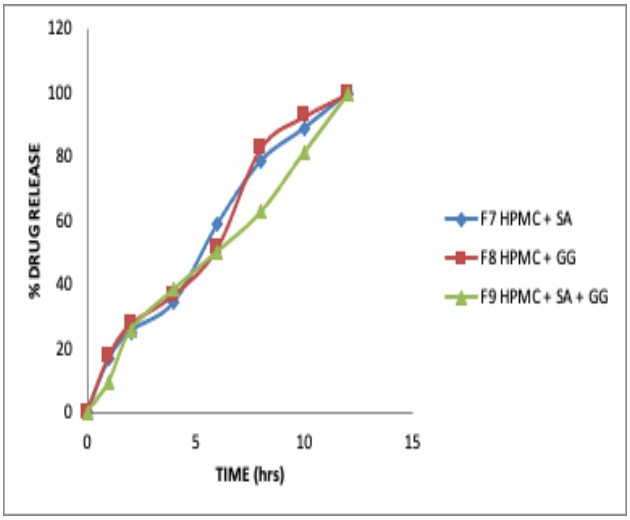

Figure 3 Zero order of F-7 F-8 and F-9 formulations of Lercanidipine

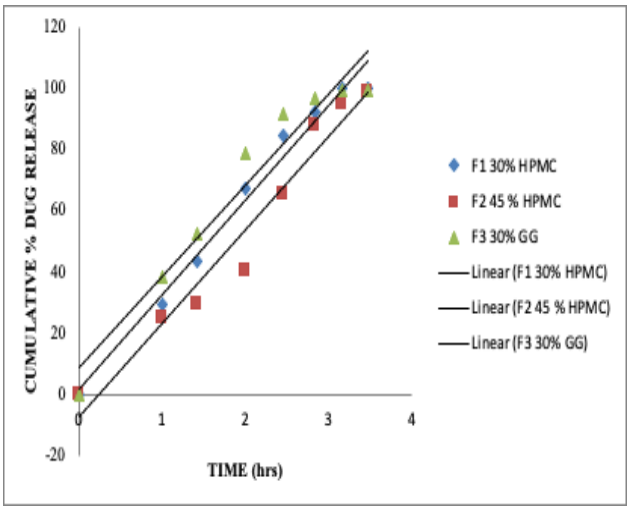

Figure 4 Higuchi plot for F-1, F-2, and F-3 formulations

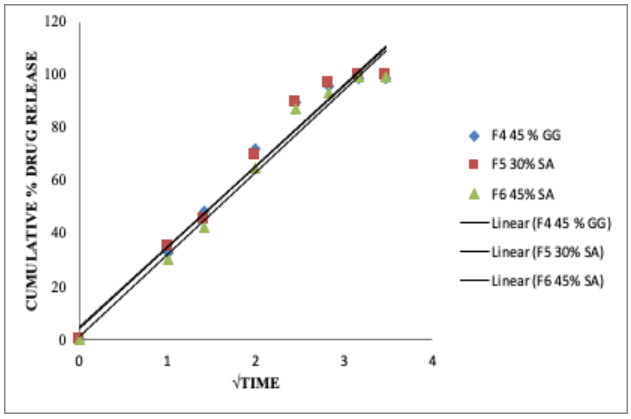

Figure 5 Higuchi plot for F-4, F-5, and F-6 formulations

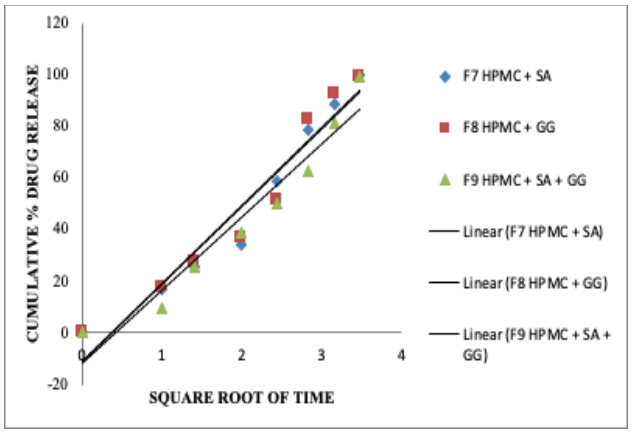

Figure 6 Higuchi plot for F-7, F-8, and F-9 formulations

CONCLUSION

The study found that as the concentration of C.R. polymer goes up, so does the order of C.R. F2 >F1(HPMC), F4 > F3 (G.G.), and F6 > F5 (S.A.). When the C.R. tablets with only natural C.R. polymers (S.A. & G.G.) were tried in both conc. (30% & 45%) no C.R. was obtained for up to 12 hours. Hence, they are not intended to be used alone for C.R. In all the C.R. polymers, 45% of HPMC(F2) is showing better C.R. for further studies to know the effect of natural C.R. polymers (S.A. & G.G.) with HPMC, the 45% OF HPMC is kept constant. (F7, F8 & F9). Out of all formulations, the 45% HPMC + 10%SA + 10% G.G. (F9) has better C.R. due to the combination of various release mechanism characters of All three polymers. The order of C.R. F9>f7>F8>from the dissolution data evident that the order C.R. It is evident that C.R. was better attained with a combination of HPMC & the two natural polymers than HPMC + single Natural polymer or an HPMC alone.

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