Research Article

FORMULATION AND IN VITRO EVALUATION OF LOVASTATIN BUCCAL TABLETS

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ABSTRACT

The present investigation is concerned with formulation and *in-vitro* evaluation of mucoadhesive buccal tablets containing anticholesteremic agent. Lovastatin to by-pass the first pass effect and to improve its bio availability with reduction in dosing frequency. The tablets were prepared by direct compression method. Fifteen formulations were developed with varying combinations of polymers like hydroxy propyl methyl cellulose (HPMC) K100M, Poly vinyl pyrrolidone (PVP) k30, Carbopol 934, Sodium carboxy methyl cellulose. The tablets were tested for weight variation, hardness, drug Content, swelling index and *in-vitro* drug dissolution study. FTIR studies showed no evidence on interactions between drug, polymers, and excipients. The *in-vitro* release of Lovastatin was performed under sink conditions (Sodium lauryl sulphate (SLS) PH 6.8, $37 \pm 0.5^\circ\text{C}$, rpm 50) using USP type II rotating paddle method. The best *in-vitro* drug release profile was achieved with the formulation F5 which contains HPMC 25 mg, CP 12.5 mg and PVP 12.5 mg. The swelling index of formulation F5 was found to be 6.56 and 78.6 respectively. The formulation F5, containing 20 mg of Lovastatin exhibited 12 h sustained drug release i.e. 98.6 % with desired therapeutic concentration.

Keywords: Lovastatin, mucoadhesive buccal tablet, HPMC K100M, PVPk30, Carbopol 934, Sodium CMC.

INTRODUCTION

Pre formulation testing is the first step in the rational development of dosage form of the drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and combined with excipients. The overall objective is that Lovastatin is a member of the drug that belongs to the class of statins used for lowering the cholesterol that is hypolipidemic agent having better bioavailability, by passing first-pass metabolism and thereby preventing cardiovascular diseases. It is the drug of choice in primary hyperlipidemias with raised LDL and total cholesterol levels as well as for secondary i.e. diabetes, nephritic syndrome hypercholestoremia. Lovastatin undergoes extensive first-pass metabolism in the liver and as a consequence of this the availability of Lovastatin in general circulation is very low and variable. In single dose study in four hypercholesterolemic patients it was estimated that less than 5 % of an oral dose of Lovastatin reaches general as well as an active inhibitor.

MATERIAL AND METHOD

Lovastatin, Symed labs limited, Hyderabad, India Phosphate buffer pH 6.8 Merck specialties Pvt Ltd, Mumbai, India (Dissolve 6.8045 g of potassium dihydrogen phosphate and 0.896 g of sodium hydroxide in sufficient water to produce 1000 ml.), Hydroxy propyl methyl cellulose K100M, Drugs India, Hyderabad, India poly vinyl pyrrolidone K30, Drugs India, Hyderabad, India Carbopol 934, Drugs India, Hyderabad, India Sodium carboxy methyl cellulose, Sd fine Chem. Ltd. Mumbai, India Ethyl cellulose, Sd fine Chem. Ltd. Mumbai, India Lactose, Sd Fine Chem. Ltd. Mumbai, India Mannitol, Sd fine Chem. Ltd. Mumbai, India Magnesium stearate, Sd fine Chem. Ltd. Mumbai, India.

Method of Preparation of Buccal Tablets

Buccal tablets containing Lovastatin were prepared by direct compression method. Various batches were prepared by changing the ratio of HPMC K 100, SCMC and PVP K 30 to

identify the most effective formulation. The drug and polymer mixture was prepared by homogeneously mixing the drug with HPMC K 100, SCMC, and PVP K-30, CP-934 (mucoadhesive polymers), Mannitol and lactose (diluents) in a glass mortar for 15 minutes. Before direct compression, the powder were screened through a 60 μm sieve and thoroughly blended. The blend was lubricated with magnesium stearate for 3-5 minutes. The mixture (100 mg) was then compressed using an 8 mm diameter die in a 9-station rotary punching machine (Ahmadabad, India). The upper punch was raised and the backing layer of EC was placed on the above compact; the two layers were then compressed into a mucoadhesive tablet. Each tablet weighed 150 mg and the compositions of Lovastatin buccal tablets were given in Table 1.^{5,6}

Drug –Polymer Compatibility Studies By FTIR

Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy). Infrared (IR) spectra were obtained on a Perkin Elmer 2000 IR system (Perkin Elmer, Norwalk, CT) using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1} . FTIR absorption spectra of pure drug and all the polymers used like HPMC, SCMC, CP, PVP, EC and the combination of drug and polymers were shows no significant interaction between drug and polymers. The spectra obtained were shown in the Figure 1 and 2.

Physico - Chemical Evaluation Thickness

The thickness of the each Tablet was measured by using vernier caliper and the average thickness was calculated.

Weight variation

Formulated Tablets were tested for weight uniformity, 20 Tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percent

weight variation was calculated by using the following formula.

Hardness

The hardness of Tablets was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm².

Friability

The Roche friability test apparatus was used to determine the friability of the Tablets.

$$\% \text{ Weight Variation} = \frac{\text{Average Weight} - \text{Initial Weight}}{\text{Average Weight}} \times 100$$

Twenty pre-weighed Tablets were placed in the apparatus and operated for 100 revolutions and then the Tablets were reweighed. The percentage friability was calculated according to the following formula.

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

Drug content uniformity was determined as triplicate by dissolving the tablets in DMSO (Dimethyl sulfoxide) and filtering with Whatman filter paper (0.45 µm, Whatman, Maidstone, UK). The filtrate was evaporated and the drug residue dissolved in 100 ml of phosphate buffer (pH 6.8). The 5 ml solution was then diluted with phosphate buffer up to 20 ml, filtered through Whatman filter paper and analyzed at 305 nm using a UV spectrophotometer.

Swelling index

The swelling index of tablets was determined by gravimetry. The swelling rate of the bio adhesive tablet was evaluated by

using 1 % agar gel plate. The average weight of the tablet was calculated (W1). The tablets were placed on gel surface in a petri dish placed in an incubator at 37 ± 1 °C. Tablets was removed at different time intervals (1, 2, 3, 4, 5 and 6 h), wiped with filter paper and reweighed (W2). The swelling index was calculated by the formula.

$$\text{Swelling Index (S.I)} = [(W2-W1)/W1] \times 100$$

Where, W1- initial weight of Tablet, W2- weight of disks at time.

In-vitro Drug Release Study

The USP type II rotating paddle method was used to study the drug release from the Tablet. The dissolution medium consisted of 900 ml of sodium lauryl sulphate (SLS) pH 6.8. The release study was performed at 37 ± 0.5 °C, with a rotation speed of 50 rpm. The backing layer of the buccal Tablet was attached to the glass slide with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. Aliquots (5 ml each) were withdrawn at regular time intervals and replaced with fresh medium to maintain sink conditions. The samples were filtered, with appropriate dilutions with sodium lauryl sulphate (SLS) pH 6.8 and were analyzed spectrophotometrically at 238 nm.^{3,4}

RESULTS

Thickness, weight variation, hardness and friability

The prepared Lovastatin buccal tablets were characterized for thickness, weight variation, hardness and friability by following the procedures as per pharmacopoeia, to check the stability of tablets during transportation, packaging and storage. The results obtained in all the formulations were within pharmacopoeial standards. The results were tabulated in Table 2.

Table 1: The Composition of Buccal Tablets of Lovastatin

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Lovastatin	20	20	20	20	20	20	20	20	20	25	20	20	20	20	20
HPMC K100	25	-	12.5	12.5	25	-	6.25	25	6.25	37.5	-	-	12.5	12.5	12.5
SCMC	12.5	25	-	25	-	12.5	6.25	6.25	25	-	37.5	-	12.5	12.5	12.5
PVP K 30	-	12.5	25	-	12.5	25	25	6.25	6.25	-	-	37.5	12.5	12.5	12.5
CP 934	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Mg.stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Lactose	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	27.5	-
Mannitol	5	5	5	5	5	5	5	5	5	5	5	5	5	-	27.5
EC	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Total wgt in mg	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150

Table 2: Physicochemical evaluation of buccal Tablets of Lovastatin

Code	Thickness (mm) ± SD	Weight variation mg ± SD	Hardness (Kg/cm ²)	Friability (%)	Drug content in mg	Surface pH ± SD
F1	2.12 ± 0.03	149 ± 1.55	4.2 ± 0.15	0.43 ± 0.025	11.57 ± 0.41	6.41 ± 0.061
F2	2.19 ± 0.02	147 ± 0.94	4.1 ± 0.25	0.54 ± 0.03	11.85 ± 0.19	6.73 ± 0.03
F3	2.11 ± 0.03	150 ± 0.81	4.3 ± 0.31	0.60 ± 0.042	11.32 ± 0.48	6.62 ± 0.026
F4	2.15 ± 0.05	148 ± 0.72	3.9 ± 0.21	0.48 ± 0.036	12.26 ± 0.41	6.79 ± 0.040
F5	2.18 ± 0.03	150 ± 0.19	4.3 ± 0.2	0.48 ± 0.01	12.45 ± 0.15	6.56 ± 0.065
F6	2.19 ± 0.04	147 ± 0.84	4.2 ± 0.26	0.51 ± 0.02	11.19 ± 0.01	6.77 ± 0.066
F7	2.13 ± 0.07	149 ± 0.38	4.2 ± 0.31	0.61 ± 0.038	12.21 ± 0.03	6.77 ± 0.061
F8	2.16 ± 0.02	148 ± 0.52	4.5 ± 0.25	0.54 ± 0.025	12.15 ± 0.65	6.56 ± 0.066
F9	2.13 ± 0.02	148 ± 0.76	4.3 ± 0.45	0.44 ± 0.01	11.74 ± 0.31	6.76 ± 0.045
F10	2.15 ± 0.02	150 ± 0.41	4.2 ± 0.41	0.44 ± 0.026	11.43 ± 0.15	6.72 ± 0.04
F11	2.21 ± 0.03	149 ± 0.82	4.4 ± 0.21	0.48 ± 0.03	12.03 ± 0.44	6.67 ± 0.045
F12	2.13 ± 0.03	147 ± 0.48	4.1 ± 0.15	0.69 ± 0.025	12.35 ± 0.61	6.64 ± 0.077
F13	2.21 ± 0.02	149 ± 0.65	4.2 ± 0.31	0.47 ± 0.015	11.89 ± 0.45	6.75 ± 0.049
F14	2.15 ± 0.01	150 ± 0.23	4.0 ± 0.41	0.44 ± 0.036	12.13 ± 0.35	6.60 ± 0.056
F15	2.16 ± 0.02	149 ± 0.57	3.7 ± 0.15	0.52 ± 0.041	11.65 ± 0.28	6.76 ± 0.080

Table 3: Swelling index data for all formulations

Code	Swelling index $\pm$ S.D					
	Time in h					
	1	2	3	4	5	6
F1	26.09 $\pm$ 0.76	38.61 $\pm$ 1.08	55.58 $\pm$ 0.80	64.96 $\pm$ 0.70	71.27 $\pm$ 0.76	74.84 $\pm$ 0.27
F2	22.23 $\pm$ 0.72	32.15 $\pm$ 0.91	40.75 $\pm$ 0.46	50.71 $\pm$ 0.54	60.04 $\pm$ 0.61	65.21 $\pm$ 0.53
F3	19.19 $\pm$ 0.64	24.48 $\pm$ 0.63	37.81 $\pm$ 0.67	45.84 $\pm$ 0.68	51.8 $\pm$ 0.66	55.77 $\pm$ 0.51
F4	23.73 $\pm$ 1.08	33.97 $\pm$ 0.48	46.13 $\pm$ 0.93	51.81 $\pm$ 0.69	63.84 $\pm$ 0.28	68.91 $\pm$ 0.93
F5	27.39 $\pm$ 1.03	41.62 $\pm$ 0.90	57.67 $\pm$ 0.53	66.68 $\pm$ 0.75	71.25 $\pm$ 0.61	78.6 $\pm$ 1.04
F6	19.81 $\pm$ 0.67	31.39 $\pm$ 0.98	39.81 $\pm$ 0.67	51.12 $\pm$ 0.62	57.52 $\pm$ 1.08	62.76 $\pm$ 0.43
F7	16.01 $\pm$ 0.84	25.64 $\pm$ 0.75	32.76 $\pm$ 0.54	41.10 $\pm$ 0.88	46.46 $\pm$ 0.87	51.76 $\pm$ 0.64
F8	26.65 $\pm$ 0.72	40.98 $\pm$ 0.79	56.93 $\pm$ 0.86	65.29 $\pm$ 0.97	71.28 $\pm$ 0.30	74.84 $\pm$ 0.60
F9	23.35 $\pm$ 1.12	31.43 $\pm$ 0.64	41.91 $\pm$ 0.93	51.66 $\pm$ 0.57	61.44 $\pm$ 0.63	65.69 $\pm$ 0.64
F10	31.47 $\pm$ 0.93	42.62 $\pm$ 0.77	58.41 $\pm$ 0.79	67.45 $\pm$ 0.96	73.17 $\pm$ 0.61	76.85 $\pm$ 0.65
F11	24.72 $\pm$ 0.38	33.98 $\pm$ 0.81	44.19 $\pm$ 0.91	51.81 $\pm$ 0.67	61.52 $\pm$ 1.06	67.85 $\pm$ 0.51
F12	17.13 $\pm$ 0.55	27.77 $\pm$ 0.61	35.96 $\pm$ 0.86	41.92 $\pm$ 0.88	48.72 $\pm$ 0.65	53.93 $\pm$ 0.75
F13	21.48 $\pm$ 0.94	32.18 $\pm$ 0.82	42.18 $\pm$ 0.37	50.91 $\pm$ 0.82	57.80 $\pm$ 0.99	64.26 $\pm$ 0.78
F14	22.3 $\pm$ 0.65	31.96 $\pm$ 0.49	43.34 $\pm$ 0.48	51.67 $\pm$ 0.49	59.15 $\pm$ 0.70	66.04 $\pm$ 0.83
F15	20.47 $\pm$ 0.76	31.11 $\pm$ 0.75	42.01 $\pm$ 0.86	48.12 $\pm$ 0.62	57.2 $\pm$ 0.40	64.08 $\pm$ 0.63

Figure 1: FTIR Spectra of Lovastatin

Figure 2: FTIR Spectra of Lovastatin + polymer mixtures (HPMC, SCMC, PVP, CP and EC)

Figure 3: Swelling index after 6 h for formulation F5

Table 4: In-Vitro drug release studies of all formulations

Time (h)	Formulation Code														
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	10.8	12.6	11.8	13.4	12.8	11.2	14.2	10.2	13.2	11.6	13.6	14.2	13.8	14.6	13.5
2	18.2	23.2	21.6	22.8	19.2	20.6	25.6	18.6	23.8	18.4	22.8	27.6	28.2	27.8	24.8
3	26.1	31.4	32.8	33.2	28.8	31.2	37.1	25.2	32.4	24.6	32.6	35.4	39.8	40.6	33.2
4	34.2	42.6	43.2	45.1	36.2	42.4	46.5	32.8	43.2	32.2	43.2	46.2	51.6	50.2	45.9
5	43.2	49.8	52.1	53.6	43.4	48.6	54.8	42.6	51.2	43.8	51.4	54.8	62.6	59.4	56.4
6	51.4	57.6	63.6	64.2	50.6	56.8	66.6	52.4	59.4	51.6	59.4	67.6	71.4	70.8	69.7
7	62.2	68.2	70.6	71.9	61.2	67.4	75.2	60.8	68.3	61.8	68.7	74.8	78.2	78.6	77.2
8	71.6	74.6	78.4	79.2	69.6	73.2	83.4	71.6	76.2	72.2	76.4	83.2	85.6	86.4	85.8
9	81.2	81.2	83.9	84.4	78.2	80.6	90.2	82.3	81.8	79.4	82.2	88.6	90.4	91.2	90.9
10	87.4	89.6	91.2	92.4	86.4	88.2	97.4	87.2	89.4	86.2	91.3	96.2	96.6	97.8	96.2
11	92.4	97.1	97.4	98.6	92.8	97.6	-	91.6	98.2	91.3	97.4	-	-	-	-
12	98.3	-	-	-	98.6	-	-	98.4	-	98.1	-	-	-	-	-

Graph 1: *In-vitro* drug release data for formulation F1-F7

Swelling index

The swelling behavior of the polymer was reported to be crucial for its bio adhesive character. The adhesion occurs shortly after swelling but the bond formed is not very strong. The adhesion increases with the degree of hydration till the point of disentanglement at the polymer tissue surface, which leads to abrupt drop in adhesive strength due to over hydration. The formulation M5 shows maximum swelling index at the end of 6 h (78.6 ± 1.04) due to the highest percentage of HPMC with Carbopol. The results were shown in the Table 3.

In-vitro drug release studies

Distinguishable difference was observed in the release of Lovastatin in all formulations. The results and data of *in vitro* studies of all formulations are shown in the Table 4 and the graph was shown in Graph 1 and Table 4.

CONCLUSION

Amongst all formulation, the formulation F5 contains HPMC 25 mg, CP 12.5 mg and PVP 12.5 mg was the best one in all the aspects. The *in vitro* release kinetics studies reveal that all formulations fits well with zero order kinetics followed by Peppas, first order and then Higuchi's model and the mechanism of drug release is non-Fickian diffusion. Lovastatin buccoadhesive tablets could be promising one as they, increase bioavailability, minimize the dose, reduces the side effects and improves patient compliance hence, Lovastatin might be a right and suitable candidate for oral sustained drug delivery via buccoadhesive tablets for the therapeutic use.

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