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RESEARCH ARTICLE

PHARMACOLOGY

DEVELOPMENT AND CHARACTERIZATION OF LOVASTATIN CONTROLLED RELEASE BUCCOADHESIVE DOSAGE FORM

DOIJAD R.C[1]., SOMPUR C.K[*2]., GOJE A.J[2], MASKE A.P[3] AND TAMBOLI F.A[4].

1 & 4. Bharati Vidyapeeth College of Pharmacy, Kolhapur, (MS), India.
2. National Institute of Medical Sciences University, Jaipur,(RJ), India.
3. Shri Balaji Shikshan Prasarak Mandal's B.Pharmacy College, Ambajogai, (MS), India.

SOMPUR C.K
National Institute of Medical Sciences University, Jaipur,(RJ), India.

***Corresponding author**

ABSTRACT

Recent years have seen an increasing interest in development of Novel mucoadhesive buccal dosage form. These are useful for the systemic delivery of drug as well as for local targeting of drug to particular region of body. Buccoadhesive tablets were prepared by direct compression method by using various mucoadhesive polymers namely Carbapol 934P, PVP K30, HPMC K4M, HPMC K100M, Colour Tartarazine and Sodium Saccharin. Prepared

KEY WORDS

Bilayer tablets, Buccal mucoadhesive tablets, Lovastatin, Carbapol 934P, Bioadhesion strength, PVP K30.

INTRODUCTION

Preformulation 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, bypassing first-pass metabolism and there by 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 wel as an active inhibitor. The goal of program was to establish the necessary physicochemical characteristics of new drug substances, to determine its kinetic release rate profile, to establish its compatibility with different excipients. Hence preformulation studies on the obtained sample of the drug include physical test and compatibility studies.

MATERIALS AND METHODS

materials:

Lovastatin USP supplied by Biocon LTD, Bangalore, HPMC K4M, HPMC K100M, from Colorcon Asia Pvt. Ltd. Goa, Carbapol 934 P, from Loba Chemie Pvt. Ltd. Mumbai, PVP K30, Magnesium steriate, Saccharin sodium, Tartarazine from Himedia Lab. Mumbai, Sod. Hydroxide and Potassium dihydrogen phosphate from E.Merk (India) Ltd. Mumbai.

Methods:

Lovastatin buccoadhesive controlled release tablets were prepared in three stages.

Stage- i: Preparation of core layer:

Weighed quantity of Lovastatin, polymers like Carbapol 934P and HPMC K4M used in respective ratios that is 1:1, 1:2, 2:1 and lubricant 2% were mixed well by trituration for 30 min using glass mortar and pestle. This mixture was weighed 100 mg separately as the core layer.

Stage-ii: Preparation of backing layer:

CP934P, PVP K30, Magnesium Steriate, Saccharin sodium and Tartarazine were mixed well using glass mortar and pestle. This mixture was weighed 100 mg separately as the backing layer. Composition of backing layer contained Magnesium steriate, CB940, PVP K30, Amaranth, Peppermint oil and saccharine sodium.

Stage-iii: Compression:

Firstly, the mixtures of drug and polymer (100 mg) are compressed using a pressure of 50kg/cm2 for 5 seconds then the upper was removed and the backing layer (100 mg) was added over the first layer and compressed at pressure 200kg/cm2 for 15 seconds. By this way bilayer tablets were prepared.

evaluation of developed buccoadhesve lovastatin tablets

weight variation:

The weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet to the average weight. The tablet meets the USP specification.

Hardness:
For this, test Monsanto hardness tester was used this test was done in triplicates and average weight was calculated and was measured in terms of kg/cm2.

Friability test:
Friability was measured the strength of tablet by using Roche Fribillator at 25 rpm for four minutes.

$$\% \text{ Friability} = \frac{\text{Initial weight of tablets} \_ \text{final weight of tablets}}{\text{Initial weight of tablets}} \times 100$$

Conventional compressed tablets that loss less than 0.5 to 1% of their weight are generally considered acceptable.

Water uptake study:
This was done on 1% agar gel plate. The tablets were placed with the core facing the gel surface and incubated for six hours at 37 ˚C .the tablets were weighed before and after standing on agar plate. From which percentage of water absorption was calculated and examined for any physical change.

Content uniformity test:
5 tablets were randomly taken and triturated using glass mortar and pestle and accurately weighed. Exact quantity of triturated powder equivalent to 20mg of drug was taken into 50ml of volumetric flask and dissolved in 50ml of volumetric flask and dissolve in minimum amount of methanol and volume was made up to the mark with phosphate buffer pH 6.6. This gives the concentration of 40mcg/ml which is in Beers range by using UV spectrophotometer at 238nm and to determine the average content from the prepared buccal tablet.

Measurement of surface ph:
A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping them in contact with 1 ml of distilled water pH 6.6 ± 0.05 for 2 hours and pH was noted by bringing the electrode in contact with the surface of the formulation and allowing it to equilibrate for one minute.

Measurement of bioadhesive strength:
In present study rat peritoneal was used as a model mucosal surface for bioadhesion testing . The two sides of the balance were balanced with a 5gm of weight on the right hand side. A fresh piece of rat peritoneal membrane was fixed with the mucosal surface upward . Using thread over the protrusion in the rubber block which is covered with inert alluminium surface, the block was then lowered into the glass container which was then filled with isotonic phosphate buffer pH 6.6 kept at 37± 1˚C. Buffer reaches the surface of mucosal membrane and keep it at moist. This was then kept below the left hand setup of the balance. The tablet was then glued at the border adhered to a alluminium surface hanging on left hand side and beam raised with 5gm weight on the right pan removed. This was lowered at the alluminium surface along with the tablet over the mucosa with weight of 5gm.

The balance was kept in this position for 10 min and then slowly weights were added to the right pan. The addition of weight was stopped as soon as the detachment two surface was obtained. The weight in pan that was total weight minus 5gm was the force required to separate the tablets from the mucosa. This give the bioadhesive strength of the tablet in gram.

Invitro release studies:
The dissolution of the buccal tablet was performed by using USP XXIII dissolution apparatus by using 900ml phosphate buffer pH 6.6 as the dissolution medium which was maintained at 37˚C and stirred at 50 rpm for 8 hours at different time interval of 30 min. The

sample then was analysed spectrophotometrically at 238nm and the cumulative amount of drug release at various time intervals was calculated.

Stability studies:
Bilayer tablet of Lovastatin formulated and accelerated stability studies were carried out as per ICH guidelines. That was stored at 40˚C / 75% RH in closed high density polyethylene bottles for 3 months. The sample was withdrawn after periods of 1 month, 2 months and 3 months. The samples were analysed for its hardness, drug content and *In Vitro* release.

RESULTS AND DISCUSSION

Weight variation:
Twenty tablets of each formulation were evaluated. Their average weights of each formulation has been recorded in table 2. The values obtained indicate that all the tablets of different formulations were within the USP specification. None of the tablet deviated ± 7.5% of total weight.

Hardness:
The tablets of each formulation were evaluated and mean hardness values are recorded in table 2. The values were found to be in the range of 5.0 to 8.0 kg/cm^2. They revealed that the tablets were having good mechanical strength.

Friability test:
The friability values are recorded in table 2. The average friability for all the formulations shown in the range of 0.0498% to 0.5734% and was less than 1% and compiled with USP specification.

Water uptake study:
The percentage water uptake of all buccal tablets containing Lovastatin is given in table 3. Comparison of water uptake for each formulation and a picture of percentage of water uptake study for each formulation were found to be 50 %, 68.88%, 37.50% for A1, A2, A3, 40.29%, 68.31%, 65.17% for B1, B2, B3 and 50.50%, 48.50%, 64.10% for C1, C2, C3 respectively. The values indicate that A3, B3, C3 showed higher water absorption compare to other formulations.

Content uniformity test:
Table 2. shows the result of drug content uniformity in each formulation. The mean drug content was found to be in the range of 92% to 107%.

Table No. 1
Composition of Buccal Tablet of Lovastatin Core layer 100 mg

Ingredients	A1	A2	A3	B1	B2	B3	C1	C2	C3
Lovastatin	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Carbapol	39 mg	26 mg	52 mg	39 mg	26 mg	52 mg	39 mg	26 mg	52 mg
HPMC K4M	39 mg	26 mg	52 mg	----	----	----	----	----	----
HPMC K100M	----	----	----	39 mg	26 mg	52 mg	----	----	----
PVP K30	----	----	----	----	----	----	39 mg	26 mg	52 mg
Magnesium steriate	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Polymer ratio	1:1	1:2	2:1	1:1	1:2	2:1	1:1	1:2	2:1

Table 2

Evaluation of Physical parameters of different buccoadhesive tablets of Lovastatin

Formulation code	Evaluation parameters					
	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Average weight (mg)	U.S.P. weight variation test	Drug Content (%)
A1	2.25	5.0	0.348	200.65	Passes	92.50
A2	2.30	6.5	0.573	200.55	Passes	95.00
A3	2.26	6.8	0.224	200.45	Passes	97.50
B1	2.24	5.0	0.174	200.30	Passes	100.00
B2	2.28	5.6	0.274	200.45	Passes	92.00
B3	2.22	6.0	0.294	200.00	Passes	102.50
C1	2.20	6.8	0.049	200.60	Passes	107.00
C2	2.28	7.5	0.474	200.25	Passes	105.00
C3	2.27	6.0	0.199	200.10	Passes	97.00

Measurement of surface ph:

The measurement of surface pH has been shown in in table 3. They found to be 6.15 to 6.80 of all formulations are all most within the range of salivary Ph that is 6.2 to 7.4, thereby showing better patient acceptability.

Measurement of bioadhesive strength:

The measurement of bioadhesive strength has been shown in table 3 for each type buccal tablet. The mean bioadhesive strength values were to be found 16.00, 14.00 15.00 gm/cm^{2}for A1, A2 and A3. This study showed that addition of higher proportions of PVP K30 was found to maximize the bioadhesive property of buccal tablets, when compared with other formulations containing HPMC K4M and HPMC K100M. Formulation C2 in the ratio 1:2 for CP934 P: PVPK30 is found to be the best ratio of these polymers and exhibited strongest bioadhesive strength. Comparison of bioadhesive strength for each formulation is shown figure 2.

Table 3

Evaluation of physical parameters of different buccoadhesive tablets of Lovastatin

Formulation	% water absorption	Surface pH	Bioadhesion strength (g/cm^2)
A1	50.00	6.23	16.00
A2	68.88	6.30	14.00
A3	37.50	5.99	15.00
B1	40.29	6.43	16.00
B2	68.31	6.38	20.00
B3	65.17	6.77	15.00
C1	51.50	6.57	17.00
C2	48.50	6.13	22.00
C3	64.10	6.24	18.00

Invitro release studies:

In Vitro dissolution was studied in phosphate buffer pH 6.6. *In Vitro* release data obtained for tablets A1, A2, A3, B1,B2,B3,C1,C2 and C3 are given in table 4. *In Vitro* dissolution studies clearly showed that the formulation containing CP 934P: HPMC K4M showed higher drug release as compared to other formulations. A2 is the best formulation selected on the basis of maximum drug release.

Stability studies:

The stability study result obtained has been shown in table 5. The Lovastatin buccoadhesive controlled release tablet did not show any significant change in physicochemical parameters and other test .Thus, it was found controlled release buccoadhesive tablet of Lovastatin were stable in above mentioned conditions for at least three months.

Table 4

Invitro release for buccoadhesive tablets of Lovastatin for formulation A2

Sl. No.	Time (h)	Vol. Withdrawn (ml)	Abs.	% CDR
1	0.5	5	0.016	13.016
2	1	5	0.044	30.901
3	2	5	0.076	50.917
4	3	5	0.078	51.712
5	4	5	0.121	78.007
6	5	5	0.123	78.430
7	6	5	0.129	81.270
8	7	5	0.136	84.636
9	8	5	0.157	96.282

Table 5

Stability Studies after 30 days Storage of selected Formulation (A2) at 4^0C, Room Temperature (RT) and 32^0C

	Formulation A2			
	Water uptake (%)	**Bioadhesive strength g/cm^2**	**Content uniformity**	**Cum drug release (%)**
At 4^0C	67.11	14.00	92.64	93.16
Room temperature	68.48	14.00	94.98	95.00
At. 37^0C and 65% RH	67.31	13.50	93.06	94.11

Fig. 1

Plot of cum % drug release Vs Time for buccoadhesive tablets of Lovastatin for formulation A2

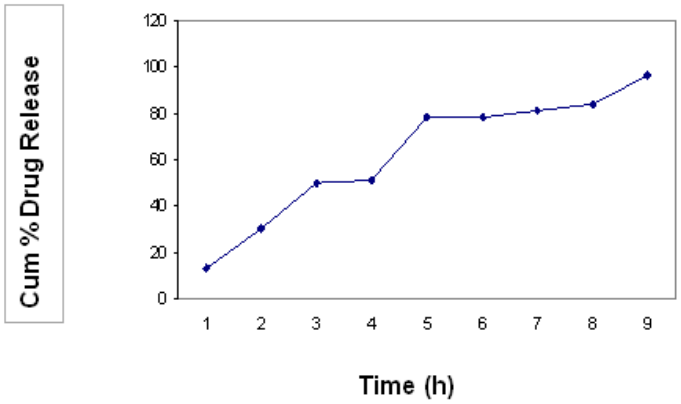


Fig. 2

Bar Graph of Bioadhesive strength for different Buccoadhesive tablets of Lovastatin

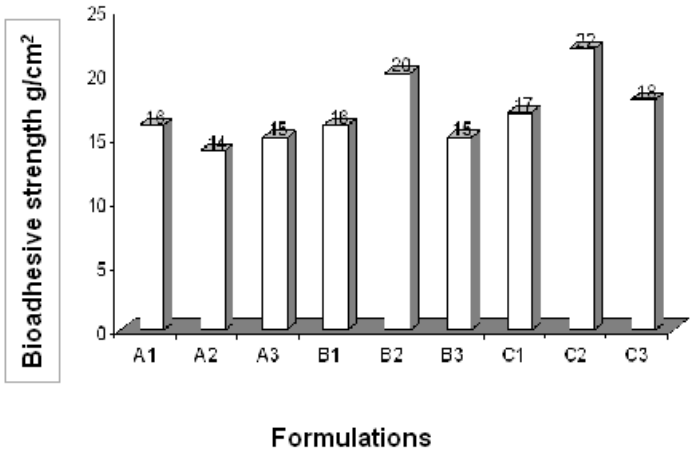
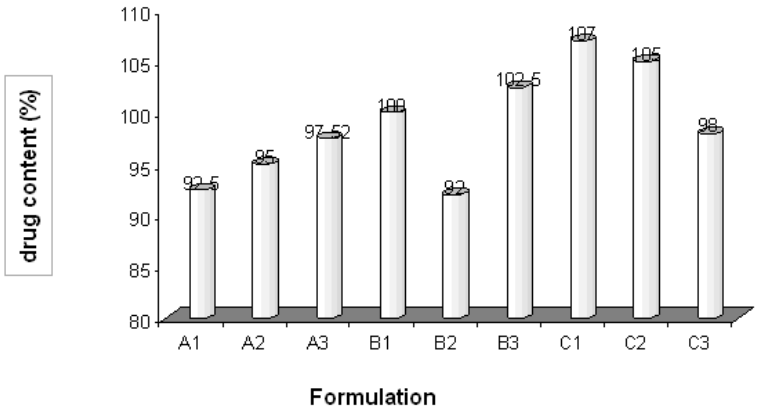


Fig 3

Bar graph of content uniformity of different Buccoadhesive tablets of Lovastatin



CONCLUSION

In the present study an attempt has been made to develop a novel buccoadhesive drug delivery system in the form of a tablet for the release of Lovastatin in unidirectional manner with improved bioavailability. Although all buccal tablets exhibited satisfying drug release, the best results were obtained with tablet of carbapol 934P in combination with HPMC K4M (1:2). *Invitro* dissolution studies of the optimized formulation shows that the present drug release was 96.28% Buccoadhesive tablets were undertaken for stability studies and result showed slight increase in drug release.The buccal formulation of Lovastatin in the form of buccoadhesive tablets were developed to satisfactory level in terms of drug release, bioadhesive strength, content uniformity, percentage water uptake, surface pH, friability, hardness and weight variation.

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