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Formulation and Evaluation of Mucoadhesive Buccal Tablets of Pravastatin Sodium

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ABSTRACT

Pravastatin sodium, a HMG-CoA reductase inhibitor, is widely used for the treatment of hypercholesterolemia. However, its low oral bioavailability (approximately 17%) due to extensive hepatic first-pass metabolism and limited gastrointestinal absorption necessitates a more efficient delivery system. This study focuses on the formulation and evaluation of mucoadhesive buccal tablets of pravastatin sodium as a promising alternative route of administration to bypass first-pass metabolism and enhance bioavailability.

Mucoadhesive buccal tablets were formulated using a direct compression method, with various mucoadhesive polymers such as Carrageenan gum, Polyvinylpyrrolidone (PVP) K30, and Pluronic F127, as well as other excipients. The tablets were designed as a bilayered system with an impermeable backing layer of ethyl cellulose to ensure unidirectional drug release towards the buccal mucosa.

Keywords :- Pravastatin sodium, HMG-CoA reductase inhibitor, Hypercholesterolemia , Hyperlipidaemia , Buccal drug delivery

INTRODUCTION

Hyperlipidaemia is a medical term for abnormally high levels of lipids or lipoproteins in the blood. The two major types of lipids found in the blood are triglycerides and cholesterol [1]. Hyperlipidaemia is an umbrella term that refers to acquired or genetic disorders that result in high levels of lipids (fats, cholesterol, or triglycerides) circulating in the blood [2]. This disease is usually chronic and requires ongoing medication to control blood lipid levels. Cholesterol is carried through the bloodstream by attaching to certain proteins. The combination is called a lipoprotein. Four different types of lipoproteins carry cholesterol in the blood: • High-density lipoprotein (HDL) or "good cholesterol." • Low-density lipoprotein (LDL) or "bad cholesterol." • Very low-density lipoproteins (VLDL), which are very bad forms of cholesterol • Chylomicrons, which carry very little cholesterol but a lot of another fat called triglycerides Hyperlipidemia predisposes a person to atherosclerosis. Atherosclerosis is the accumulation of lipids, cholesterol, calcium, and fibrous plaques within the heart's artery walls. This accumulation narrows the blood vessel and reduces blood flow and oxygen to the muscles of the heart. Over time, fatty deposits can build up, hardening, and narrowing the arteries until organs and tissues don't receive enough blood to function correctly. If arteries that supply your heart with blood are affected, a person might have angina (chest pain). Complete blockage of the artery causes infarction of the myocardial cells, also known as a heart attack. The fatty buildup in the arteries can also lead to stroke if a blood clot blocks blood flow to the brain [3]

Classification of Hypolipidemic Drugs

A. HMG CoA Reductase Inhibitors Lovastatin, Mevastatin, Pravastatin, Simvastatin, Rosuvastatin, Atorvastatin, Fluvastatin, Cerivastatin

B. Fibric Acids Derivatives (also called fibrates) Clofibrate, Fenofibrate, Bezafibrate, Ciprofibrate, Gemfibrozil

C. Bile Acid Binding Resins Cholestyramine, Colestipol, Colesevelam, Butylated Hydroxytoluene, Probucol

D. Nicotinamides Nicotinic acid, Nicfuranose, Acipimox,

E. Cholesterol Absorption Inhibitors Ezetimibe, Gugulipid

F. Fish Oils Omega-3 marine triglycerides.

HMG CoA REDUCTASE INHIBITORS (STATINS)

Statins are hypolipidemic drugs that block the enzyme HMG-CoA (5-hydroxy-3 methylglutaryl-coenzyme A) reductase, required for the synthesis of cholesterol (Fig 1.1). Examples of statins include simvastatin, pravastatin, and lovastatin. Statins are generally quite safe, but side effects may include muscle pain and fatigue.

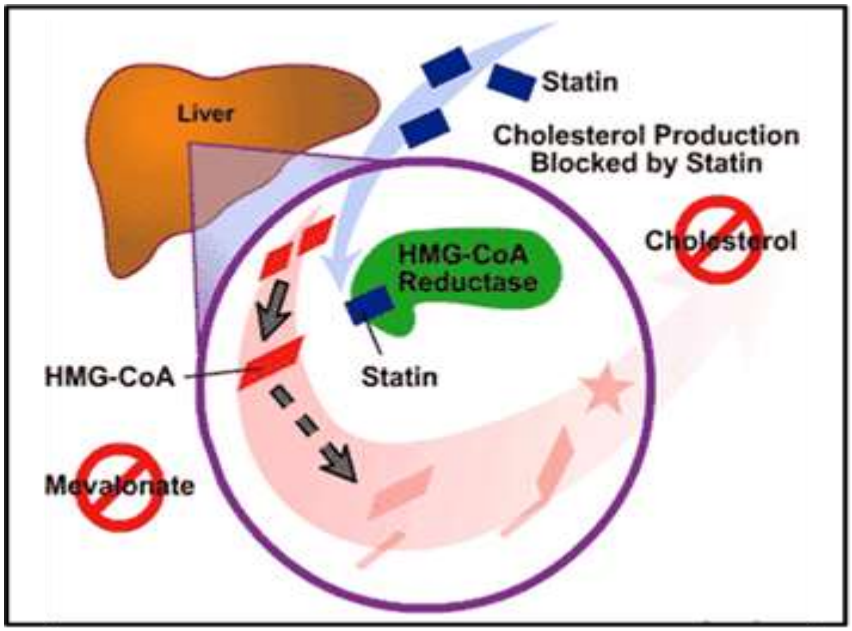


Fig :- Mechanism of Action of HMG CoA Reductase Inhibitors (Statins)

Therapeutic doses reduce CH synthesis by 20–50%. This results in a compensatory increase in LDL receptor expression on liver cells → increased receptor-mediated uptake and catabolism of IDL and LDL. Over the longterm, feedback induction of HMG-CoA

reductase tends to increase CH synthesis, but a steady-state is finally attained with a dose-dependent lowering of LDL-CH levels. Different statins differ in their potency and maximal efficacy in reducing LDL-CH. The daily dose for lowering LDL-CH by 30–35% is lovastatin 40 mg, pravastatin 40 mg, simvastatin 20 mg, atorvastatin 10 mg, rosuvastatin 5 mg. Hepatic synthesis of VLDL is concurrently reduced, and its removal from plasma is enhanced. Because HMG-CoA reductase activity is maximum at midnight, all statins are administered at bedtime to obtain maximum effectiveness. However, this is not necessary for atorvastatin and rosuvastatin, which have long plasma t½.

DRUG AND EXCIPIENTS PROFILE

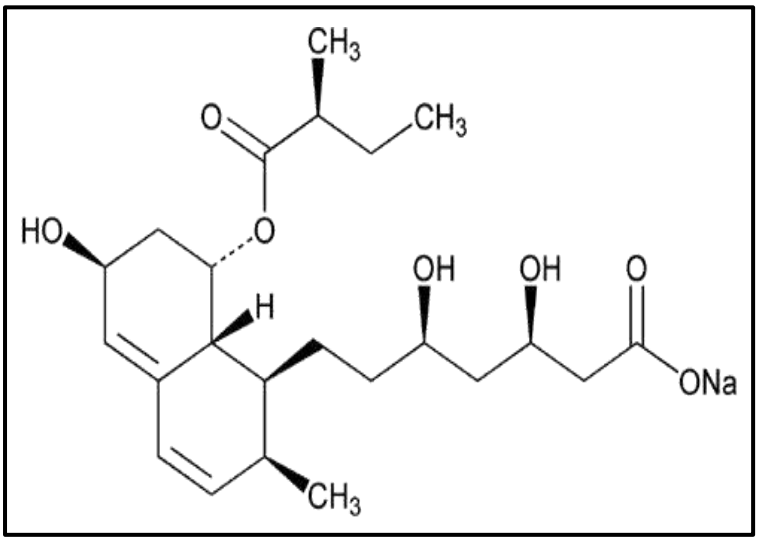


Fig Chemical structure of Pravastatin Sodium

Molecular Formula:C23H35NaO7

Chemical Name: sodium; (3R,5R)-7-[(1S,2S,6S,8S,8aR)-6-hydroxy-2-methyl-8-[(2S)-2- methylbutanoyl]oxy-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxyheptanoate.

Molecular Weight : 446.5gm/mol

Melting Point Range : 171^0C

Partition coefficient : 0.59

Description: Odorless, white to off-white, fine or crystalline powder, hygroscopic in nature.

Solubility: It is soluble in methanol and water, slightly soluble in isopropanol and practically insoluble in acetone, acetonitrile, chloroform and ether.

Category: HMG Co-A reductase inhibitor, anticholesteremic agent.

Half life: 1-3 hrs

Bioavailability: 17%

Dose: 40 mg per day.

MATERIALS AND METHOD

Table: 5.1 Materials and their sources

S. No.	Ingredients	Sources
1.	Pravastatin Sodium	Triveni Chemicals Vapi
2.	Chitosan	LOBA ltd.
3.	PVP K30	Hi Media Chem. Pvt. Ltd.
4	HPMC K4M	Qualigens
5	Xanthan gum	LOBA ltd.
6	MCC	S.D. Fine Chemicals
7	Lactose	S.D. Fine Chemicals
8	Talc	S.D. Fine Chemicals
9	Magnesium Stearate	S.D. Fine Chemicals

Table: 5.2 Equipments used in formulation

S.no	Equipment name	Company name
1	UV spectrophotometer	Shimadzu UV-1800
2	FTIR	IRAffinity-1 Shimadzu
3	Dissolution apparatus	Electrolab TDT-06L
4	Friability test apparatus	Rolex
5	Hardness tester	Monsanto
6	Tablet punching machine	Rimek mini press- IIMT
7	Physical balance	Shimadzu ATX224

PREFORMULATION STUDY

Preformulation study is the foundation of formulation development of any candidate drug. It provides complete information of pharmaceutically significant physicochemical properties of the selected drug. The objective of preformulation study is to select appropriate polymorphic form of the drug, analyze its physicochemical properties and present a comprehensive knowledge of its stability under various conditions that are useful for the development of an optimum dosage form. The preformulation testing is the first step in the development of dosage forms of a drug substance. These investigations may confirm that there are no significant barriers to dosage form development. Pravastatin Sodium was obtained as a gift sample from Triveni Chemicals Vapi, Gujrat, India.

PHYSICAL APPEARANCE: PVS was found to be a white, odourless crystalline powder (Table 5.3)

DRUG IDENTIFICATION:

Following tests were performed to identify PVS.

A. FTIR of PVS

KBr pellet technique was followed for this study. In this, the sample and the KBr were taken in 1:300 ratios. The mixture of sample and KBr was triturated to make a fine powder. The fine powder was made into pellets by using pelletizer. The transparent pellets were placed in the Perkin Elmer FT-IR spectrometer, and the spectrum was recorded (Table 5.4 & Fig 5.2).

A. Melting Point

The required amount of drug was taken in a capillary tube, and then the capillary tube was kept in a melting point apparatus. The melting point was determined by using LAB INDIA melting point apparatus (Table 5.3).

B. Determination of wavelength maxima (λmax)

PVS (100 mg) was accurately weighed and dissolved in 10ml of PBS pH 6.8 in a volumetric flask, and the final volume was adjusted to 100ml with PBS pH 6.8. 10 ml of

this solution was further diluted to 100ml to prepare a stock solution of 100µg/ml concentration. Further, 1ml of stock solution was diluted up to 10ml PBS pH 6.8 to yield a theoretical concentration of 10µg/ml. The solution (10µg/ml) was scanned in the range 200-400 nm in a UV-Visible spectrophotometer (Shimadzu 1601, Japan) to determine the wavelength maxima [Fig. 5.3].

SOLUBILITY STUDIES

Equilibrium solubility was determined at room temperature, for this, systems of each solvent (methanol, 0.1N HCl, 0.1N NaOH, water, chloroform & acetonitrile) were taken individually in volumetric flask and drug was added gradually in each solvent and vigorously shaken on shaker (Table 5.5). As the saturation point was reached a pinch of drug was added to it and the flask was shaken for 15min and placed in the flask shaker for 24 hrs. After 24 hrs it was removed and observed. Since un-dissolved drug was found it was kept for 24hrs undisturbed. After 24 hrs, the solution was filtered and diluted suitably with reagent blank and absorbance was taken against reagent blank and recorded.

PARTITION CO-EFFICIENT OF PVS IN N-OCTANOL: WATER SYSTEM

The partition coefficient indicates the polar and non-polar nature of the drug. 100 mg of PVS was added in a mixture of distilled water (10 ml) and then n-octanol (10 ml) in a glass-stoppered test tube and shaken for 4 hr. The aqueous phase was then separated using a separating funnel, and PVS content was estimated spectrophotometrically. The content of PVS in octanol layer was calculated using the initial content taken and content in distilled water. The partition coefficient of PVS was calculated as follows (Table 5.6). Po/w = Co/Caq where, Po/w = partition coefficient of drug, Co= concentration of drug in n-octanol, Caq=concentration of drug in aqueous phase i.e. Distilled water**.**

PREPARATION OF CALIBRATION CURVE

A calibration curve was prepared spectrophotometrically based on UV absorption at λmax 239 nm in PBS pH 6.8 for the quantitative estimation of the drug. 100 mg PVS was accurately weighed and placed in a 100 ml volumetric flask to prepare a 1mg/ml solution in 100ml PBS pH 6.8. 10 ml of this solution was added to 100 ml of PBS pH 6.8 to yield a theoretical concentration of 100µg/ml. Diluents of 2 to 20µg/ml were prepared and measured at λmax 239nm. Calibration curve of PVS was made using concentration vs. absorbance data (Table 5.7 and Fig. 5.3).

DRUG-EXCIPIENTS COMPABILITY STUDIES:

Compatibility of PVS and with the excipients proposed to be used in the development of buccal mucoadhesive tablets was assessed. The experiment was conducted for pure PVS and physical mixture of the drug and various excipients (1:1 ratio). The mixtures are transferred into glass vials, sealed and kept at kept at room temperature, cold conditions and at 40ºC±2ºC/75%±5% RH for four weeks. At predetermined time intervals, samples were analyzed for physical and chemical incompatibilities (Table 5.8).

RESULTS AND DISCUSSION

Identification studies showed that the drug supplied by Pharmaceutical companies matched with the reported official standards [62]. The absorption maximum of PVS in PBS pH 6.8 was found to be 239 nm (Fig. 5.1). λmax found to be very near the λmax reported in reference books. The melting point of the drug was found to be similar to the published in reference books [61]. The solubility profile of PVS showed its hydrophilic nature and was insoluble in chloroform and acetonitrile but freely soluble in methanol, 0.1N HCl, 0.1N NaOH and water (Table 5.5). The partition coefficient was found according to the solubility profile that was indicating the hydrophilic nature of the drug (Table 5.6). PVS was studied for compatibility with excipients in different environmental conditions (Table 5.8). No drug interaction was observed during the time period of storage, showing their compatibility with all ingredients. All of the above observations confirmed the identity of drugs. Along with this, the calibration curves of both drugs were prepared. The data of calibration

curves were linearly regressed, and the equation of the straight line for the standard curve as well as correlation coefficients was determined. The correlation coefficient for standard curves was found to be very near to one, which indicates an excellent co-linear correlation between concentration 2-20 µg/ml and absorbance (Table 5.7 and Fig. 5.3). Hence, drug is following the Beer-Lambert Law in the range of 2-20 µg/ml.

Table 5.3: Physical identification tests of drugs

Parameters	Fexofenadine HCl
Physical Appearance	White crystalline powder
Melting point	140^0C

Table 5.4: Important band frequencies in FTIR spectrum of PVS

Characteristic Group	**IR Absorption Band**	
	Theoretical Peaks (cm^1)	**Practical Peaks (cm^{-1})**
C=C	1400- 1600	1580
-C-H	2840- 2950	2850
-OH	3200- 3400	3342
-C=O	1720- 1740	1728
-COOH	3600- 2500	2933

Table 5.5 Solubility of PVS in different solvent systems

Solvents	**Solubility (PVS)**
Distilled Water	100mg/0.5ml (Freely Soluble)
Chloroform	5mg/100ml (Insoluble)
0.1 N HCl	100mg/0.5ml (FreelySoluble)
0.1 N NaOH	100mg/0.5ml (Freely Soluble)
Acetonitrile	5mg/100ml (Insoluble)
Methanol	100mg/0.5ml (Freely Soluble)

Table 5.6 Partition coefficient of PVS in n-octanol: water

Drug	**Amount of Drug (mg)**		**Partition coefficient (Po/w)**
	Aqueous Phase	**n- Octanol**	**0.567**
PVS	6.38	3.62	

Table 5.7 Calibration curve of PVS in 0.1N HCL

Concentration (µg/ml)	**Absorbance**	**Statistical Parameters Regressed**
2	0.0942	
4	0.1784	**Correlation Coefficient**
6	0.2853	
8	0.3550	$r^2 = 0.999$
10	0.4542	
12	0.5513	**Line Equation**
14	0.6296	

Concentration (µg/ml)	**Absorbance**	**Statistical Parameters Regressed**
16	0.7208	y = 0.045x + 0.003
18	0.8112	
20	0.9098	

Table 5.8 Drug excipient compatibility study for 4 Weeks

Name of drug/excipients	**Initial Description**	**Test parameters**		
		Refrigerator (2-8°C)	**Room temperature**	**40°C± 75%RH**
PVS	White Powder	**No Change**	**No Change**	**No Change**
PVS + Chitosan	Off White Powder	**No Change**	**No Change**	**No Change**
PVS + Xanthan gum	Off white Powder	**No Change**	**No Change**	**No Change**
PVS + HPMC	White Powder	**No Change**	**No Change**	**No Change**
PVS + PVP K30	Off white Powder	**No Change**	**No Change**	**No Change**
PVS + MCC	White Powder	**No Change**	**No Change**	**No Change**
PVS+ Chitosan+ Xanthan gum+ HPMC+MCC+PVP	Off white Powder	**No Change**	**No Change**	**No Change**

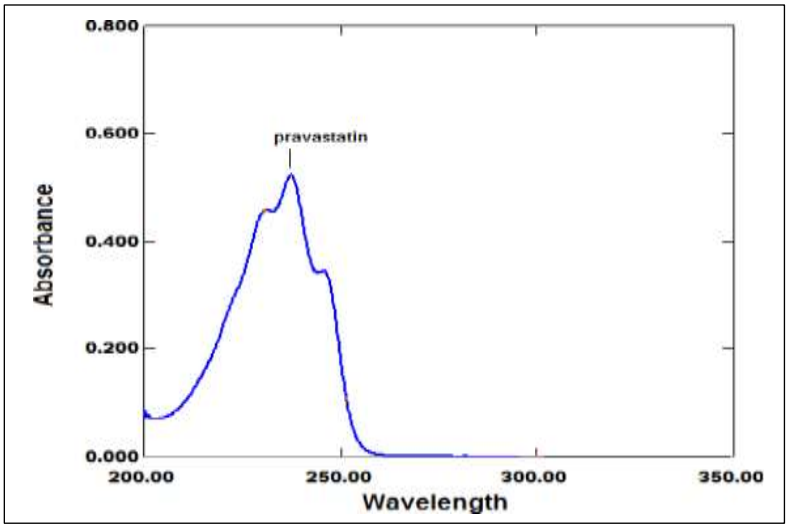


Fig. 5.1 UV-Visible Scan of PVS

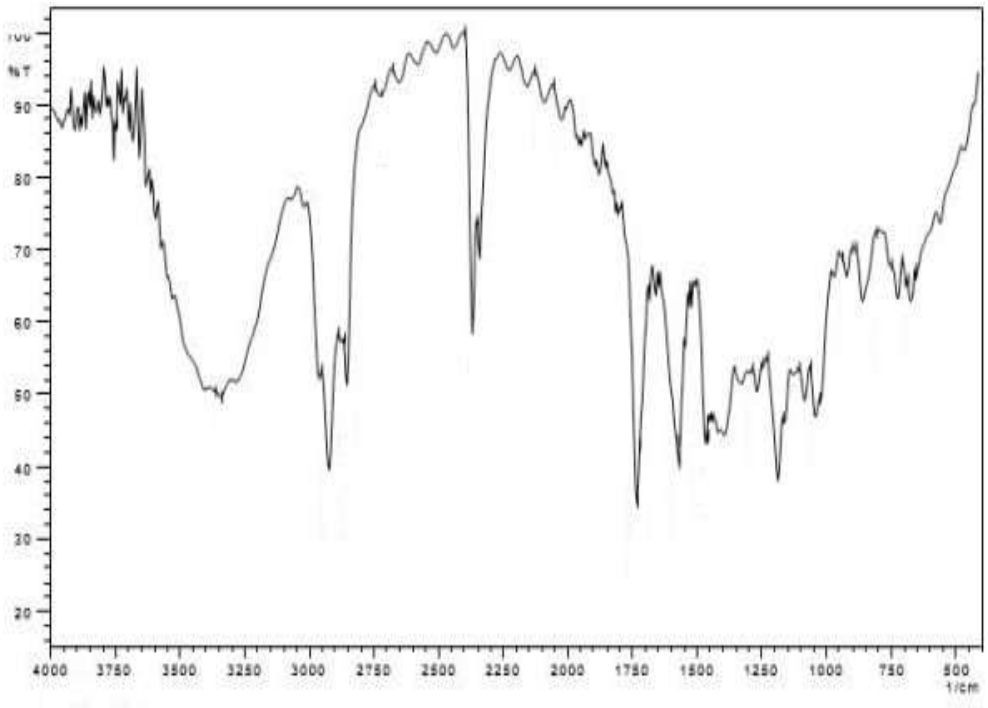


Fig. 5.2 FTIR spectra of PVS

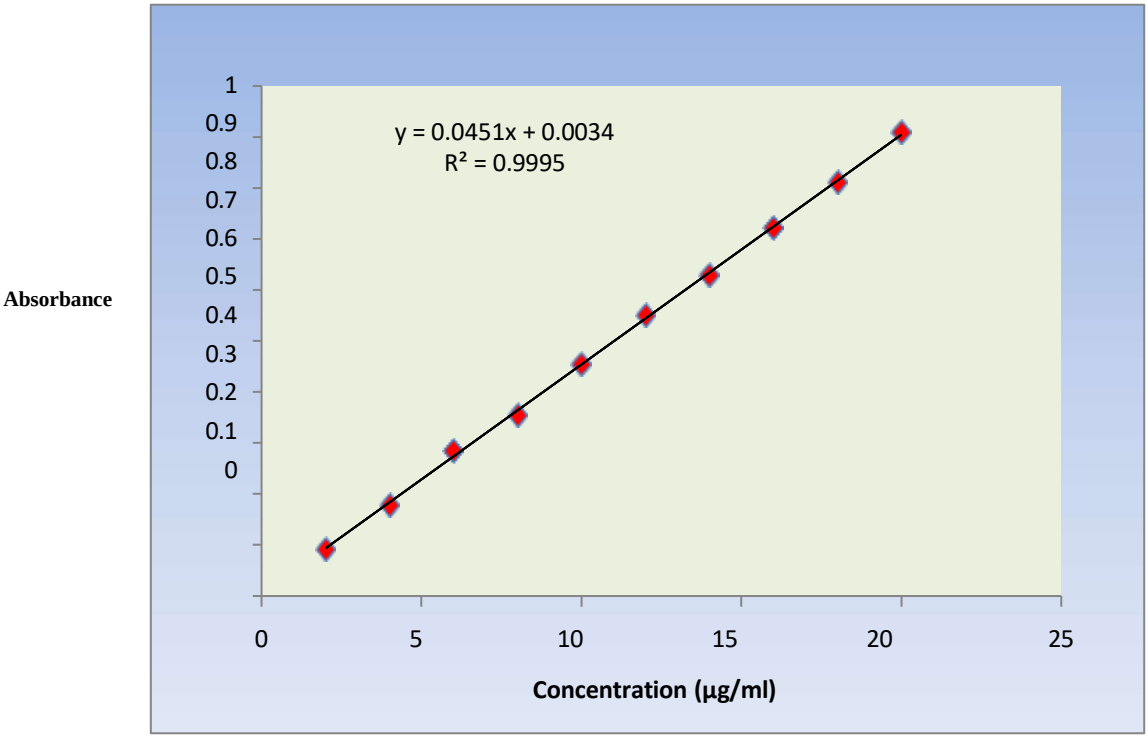


Fig. 5.3 Calibration curve of PVS

PREPARATION OF MUCOADHESIVE TABLETS OF PRAVASTATIN SODIUM (PVS):

Direct compression method was employed to prepare buccal tablets of PVS using, chitosan, HPMC K4M, and xanthan gum as bio-adhesive polymers. All the ingredients including drug, polymer and excipients were weighed accurately according to the batch formula (Table 6.1). The drug and all the ingredients except lubricants were taken on a butter paper with the help of a stainless steel spatula and the ingredients were mixed. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. The prepared blend of each formulation was pre-compressed using tablet punching machine (Rimek Press Minipress II MT, Ahmedabad).

Table-6.1 Formulation of mucoadhesive buccal tablet of Pravastatin Sodium

Ingredients mg/tablet	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Pravastatin Sodium	40	40	40	40	40	40	40	40	40
Chitosan	25	50	75	-	-	-	-	-	-
HPMC K4M	-	-	-	25	50	75	-	-	-
Xanthan gum	-	-	-	-	-	-	25	50	75
PVP 30	8	8	8	8	8	8	8	8	8
Lactose	40	25	10	40	25	10	40	25	10
MCC	34	24	14	34	24	14	34	24	14
Mg. Stearate	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1
Total	150	150	150	150	150	150	150	150	150

EVALUATION OF PREPARED BUCCAL TABLETS OF PVS

Hardness

Tablet hardness testing, is the test to determine the breaking point and structural integrity of a tablet "under conditions of storage, transportation, and handling before usage". The breaking point of a tablet is based on its shape. Tablet requires a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the buccal tablets of PVS was determined using Monsanto hardness tester [65].

Weight variation

All tablets, where the active ingredient comprises a major part of the tablet are required to meet a weight variation test. It is assumed that providing the weight of the tablet is kept within defined limits that the amount of active drug available to the user will remain the same. Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual weights deviated from the average weight by more than limit [66].

Friability (F)

Friability is the tendency for a tablet to chip, crumble or break following compression. This tendency is normally confined to uncoated tablets and surfaces during handling or subsequent storage. Friability is the loss in weight of tablet in the container due to removal of fine particle from their surface. The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (%). 20 tablets were initially weighed (initial weight) and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 mins. The tablets were weighed again (final weight). The % friability was then calculated by the following formula:

$$F = \frac{\text{Initial Weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Thickness

The weight of a compressed tablet is dependent on diameter and thickness of the tablet. In theory, the thickness of the tablets was measured using Digital Vernier Caliper. It is expressed in mm.

% Drug Content

Five tablets were powdered in a glass mortar and the powder equivalent to 50 mg of drug was placed in a stoppered 100 ml conical flask. The drug was extracted with 40 ml distilled water with vigorous shaking on a mechanical shaker (100 rpm) for 1 hour. The above content was filtered and after suitable dilutions it was analyzed in UV- spectrophotometer at 239nm using distilled water as blank [66].

Surface pH study:

The surface pH of the buccal tablets is determined in order to investigate the possibility of irritation to buccal mucosa. A combined glass electrode is used for this purpose. The tablet is allowed to swell by keeping it in contact with 1 ml of phosphate buffer pH 6.8 for 2 h at room temperature. The pH is identified by bringing the electrode into contact with the tablet surface and allowing to equilibrate for 1 min.

Swelling Index:

The swelling index of the buccal tablet was evaluated in phosphate buffer pH 6.8. The initial weight (W1) of the tablet was determined and then tablet was placed in 6 ml phosphate buffer pH 6.8 in a petridish and then was incubated at 37±1ºC. The tablet was removed after 120min and reweighed (W2). The swelling index is calculated by the formula:

$$\% \text{ Swelling index} = (W2 - W1) / W1 \times 100$$

In vitro drug release study:

The study was carried out in USP tablet dissolution test apparatus-II (Electrolab), employing paddle stirrer at 50 rpm and 250 ml of phosphate buffer pH 6.8 as dissolution medium maintained at 37±0.5^{0}C. The tablet was supposed to release drug from one side only hence a one side of tablet was fixed to glass disk and placed at the bottom of the dissolution vessel. At different time interval 0.5 ml of sample was withdrawn and replaced with fresh medium. The samples were filtered through 0.25 μm membrane filter paper and analyzed for PVS after appropriate dilution at 239nm using UV-Visible spectrophotometer.

Mucoadhesion strength:

Mucoadhesive strength of the tablet was measured by modified physical balance. The apparatus consist of a modified double beam physical balance in which an additional weight has been added to the right pan, to make the right side weight equal with the left side weight. Fresh goat intestine mucosa was washed with distilled water and then with phosphate buffer pH 6.8. The underlying mucous membrane was separated using surgical blade and washed thoroughly with phosphate buffer pH 6.8, and tied over the glass slide and under the left pan with the help of the thread. The buccal tablet was then stuck to glass stopper from one side membrane using an adhesive (Feviquick).

A preload was kept over the left pan until contact between the mucosa and the tablet was established. Now the preload was removed and weight on the right side of the pan was added. The addition of the weight on the right pan was stopped when mucoadhesivetablet detached from the goat intestine mucosa of the pan. The weight required to detach the mucoadhesive tablet from intestinal mucosa was noted as mucoadhesive strength in grams.

STABILITY STUDIES

The stability study of the formulated buccal tablets was carried out at 40±2°C for a period of 90 days. The films were characterized by drug content during the stability study period [63-65]. Sufficient numbers of tablets were individually wrapped using aluminium foil and packed in amber colour screw cap bottle and kept in stability chamber for 3 months. Samples were taken at each month interval for evaluation of drug content.

RESULTS AND DISCUSSION

A recent advance in novel drug delivery system aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. The aim of the present study was to develop buccal tablets, containing PVS, using various bioadhesive polymers such as chitosan, HPMC K4M, and xanthan gum. The buccal tablets were prepared by direct compression method. The effect of the nature of polymers was studied by preparing various formulations of buccal tablets. In all these formulations, a constant amount of drug (40 mg) was maintained. The characterization and evaluation of prepared buccal tablets were done for various parameters like hardness, friability, weight variation, thickness, drug content uniformity, mucoadhesive property, in vitro dissolution and stability studies.

EVALUATION OF PHYSIOCHEMICAL PARAMETERS

Different formulations (F1, F2, F3, F4, F5, F6, F7, F8 and F9) were prepared using chitosan, HPMC K4M and Xanthan gum and in different concentrations to study the effect of polymers/concentration on the physicochemical properties.

The weight of the tablets was found to be uniform in all the prepared batches. The weight of the buccal tablets was found to be in the range of 148.6mg to 151.2mg which ensured uniform distribution of the drug in all the formulations (Table 7.1). The values of weight variation were found to be in the acceptable range. The average percentage deviation of 20 prepared buccal tablets was less than ±5%. The thickness of buccal tablets F1 to F9 was found to be 2.25 to 2.95mm. The readings (thickness) of all the formulations fell in the acceptable range of USP standards. From the results obtained for all formulations, it can be concluded that the uniformity was achieved during the formulation (Table 7.1).

The percentage of drug content for different formulations was calculated, and the results were shown in Table 7.5. The percentage of drug content of F6 was found to be 99.86% while the formulations showed the percentage of drug content 92.12-99.86%. The drug content of tablets should be complying with the limit as 85-110% as per IP specifications. The hardness and percentage friability of the prepared buccal tablets ranged from 4.2 to 5.3kg/cm² and 0.43% to 0.71%, respectively. All the values of the physicochemical parameters are shown in Table 7.1. The surface pH for all the buccal tablets was from 6.58 to 7.24 which were nearer to salivary pH (6.5-7.5) suggesting that the prepared buccal tablets can be used without the risk of mucosal irritation and discomfort (Table 7.2).

The swelling behaviour of a mucodhesive system is an important property for uniform and prolonged release of drug and mucoadhesion. The swelling behaviour depends upon nature of polymer, concentration of polymer and pH of the medium. The swelling of all the tablets was increased as the time proceeds because the polymer gradually absorbs water due to hydrophilicity of the polymer. The percentage swelling for the buccal tablets F1 to F9 were calculated and found to be in the range of 20.41 to 58.13% in 2hrs, with formulation F6 showing a maximum of 58.13%. As the concentration of chitosan increased the swelling was decreased because of more viscous layer formation. From the results of the swelling studies, the tablets did not show any appreciable change in shape and nature during the 2h of study (Table 7.2).

The mucoadhesive strength of prepared mucoadhesive buccal tablet was studied using goat buccal mucosa and the mucoadhesive parameters are represented in Table 7.2 and Fig 7.1. The mucoadhesive strength is affected by molecular weight of polymer, contact time with membrane and degree of swelling of the polymer. The maximum 9.42g mucoadhesive strength was observed with formulation containing HPMC K4M 8.55g with xanthan gum and 5.86g with chitosan.

The in vitro release of PVS was performed in phosphate buffer pH 6.8. The in vitro release of drug was mainly affected by drug polymer ratio, nature and amount of polymer and swelling property. The buccal tablets containing chitosan alone showed initially a rapid burst release of the drug followed by > 90% release within 4 h. The chitosan rapidly hydrated and swelled to form a gel like layer through which water soluble drugs are released. The buccal tablets containing HPMC K4M showed a maximum release of 68.15% to 78.78% because HPMC with a grade of K4M has a hydrophilic gel forming matrix which was used as a release retardant. The formulations containing xanthan gum showed a maximum release of >90% within 6 h depicted that xanthan is a highly swellable polymer and rapidly get eroded in aqueous media (Table 7.3/7.4/7.5 and Fig 7.2/7.3/7.4).

STABILITY STUDY

The short term stability study was performed as per ICH guidelines using selected buccal tablets for a period of 3 months. The tablets were periodically evaluated for drug content and the results are represented in Table 7.6. The evaluated parameters did not show any significant change during the time course of storage confirmed that the prepared buccal tablets were stable.

Table-7.1 Evaluation parameters of mucoadhesive buccal tablets of PVS

Formulation code	Hardness (kg/cm^2)	Thickness mm)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	4.7±0.02	2.25±0.02	148.6±0.26	0.59±0.01	92.12±0.56
F2	4.5±0.07	2.45±0.06	149.1±0.29	0.62±0.01	93.01±0.46
F3	4.2±0.05	2.75±0.06	149.6±0.83	0.58±0.01	98.75±0.88
F4	5.3±0.06	2.55±0.06	150.6±0.12	0.56±0.00	99.21±0.34
F5	5.2±0.03	2.70±0.06	149.6±0.25	0.52±0.01	98.58±0.38
F6	5.0±0.02	2.85±0.01	149.8±0.65	0.71±0.03	99.86±0.88
F7	5.1±0.07	2.90±0.06	149.1±0.72	0.43±0.01	93.63±0.83
F8	5.0±0.05	2.95±0.01	150.6±0.40	0.68±0.01	98.89±4.00
F9	5.1±0.02	2.90±0.02	151.2±0.20	0.56±0.02	99.72±0.38

(n=3, Mean±SD)

Table-7.2 Surface pH, % Swelling and Mucoadhesive Strength of buccal tablets of PVS

Formulation code	Surface pH	% Swelling	Mucoadhesive Strength (g)
F1	6.91±0.09	41.12±0.78	5.15±0.27
F2	7.02±0.17	30.53±0.25	5.48±0.45
F3	6.78±0.79	20.41±0.40	5.86±0.60
F4	6.58±0.17	58.13±0.86	7.82±0.85
F5	6.96±0.12	46.84±0.91	9.01±0.30
F6	6.85±0.11	30.45±0.17	9.42±0.85
F7	7.24±0.06	44.52±0.18	7.35±0.47

Formulation code	Surface pH	% Swelling	Mucoadhesive Strength (g)
F8	7.00±0.10	36.84±0.86	7.98±0.75
F9	6.96±0.09	21.95±0.23	8.55±0.69

(n=3, Mean±SD)

Table-7.3 In vitro release data of PVS from mucoadhesive buccal tablets (F1-F3)

Time (hrs)	Cumulative % PVS release		
	F1	F2	F3
0.5	19.36±0.55	19.09±0.72	8.49±0.46
1	34.36±0.25	32.06±0.54	31.55±0.91
2	64.71±1.46	59.25±1.12	54.72±0.47
4	99.58±1.65	98.19±1.07	94.52±1.45

(n=3, Mean±SD)

Table-7.4 In vitro release data of PVS from mucoadhesive buccal tablets (F4-F6)

Time (hrs)	Cumulative % PVS release		
	F4	F5	F6
0.5	8.74±0.35	8.32±0.19	7.64±0.18
1	22.07±1.25	21.55±0.56	21.02±0.81
2	37.12±1.36	36.55±1.57	35.88±1.31
4	56.18±1.65	54.23±1.65	51.17±1.11
6	69.28±1.59	65.23±1.59	60.92±1.74
8	79.18±2.21	71.64±2.25	69.45±1.32

(n=3,Mean±SD)

Table-7.5 In vitro release data of PVS from mucoadhesive buccal tablets (F7-F9)

Time (hrs)	Cumulative % PVS release		
	F7	F8	F9
0.5	18.81±0.36	17.93±0.45	15.48±0.44
1	35.21±0.29	34.57±2.22	30.71±1.38
2	51.27±1.72	50.14±1.33	45.29±1.24
4	80.25±3.51	78.83±1.89	69.91±1.55
6	91.74±1.32	88.24±3.20	79.81±2.48
8	99.41±1.18	96.34±2.96	88.22±2.82

(n=3, Mean±SD)

Table-7.6 Stability study of mucoadhesive buccal tablets of PVS

Formulation	Parameter	Initial	1month	2 months	3 months
F3	%Drug Content	98.75	98.28	97.64	96.55
F6		99.86	99.25	98.36	97.85
F9		99.72	98.72	98.06	97.23

Fig 7.1 Effect of polymer concentration on mucoadhesive strength of buccal tablet of PVS

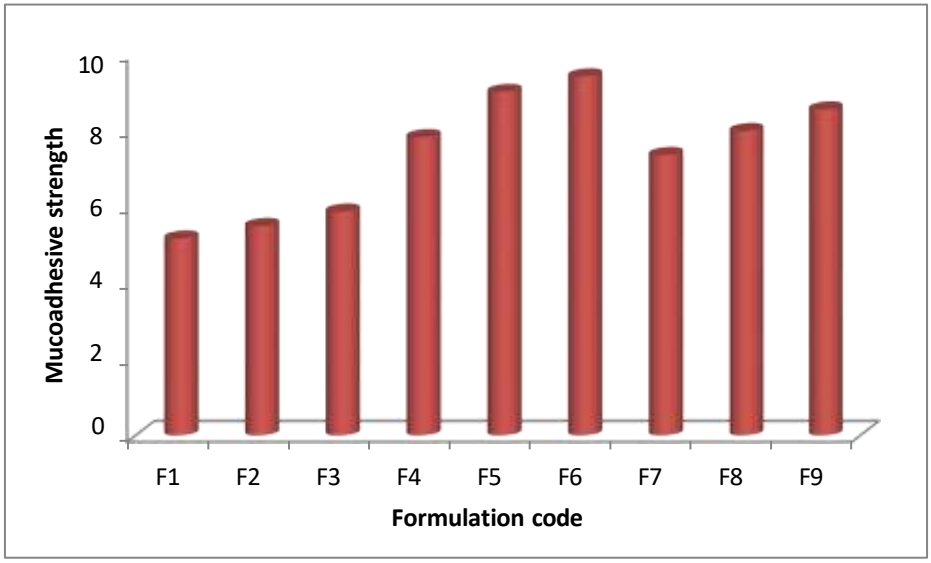


Fig 7.2 In vitro release profile of PVS from mucoadhesive buccal tablets (F1-F3)

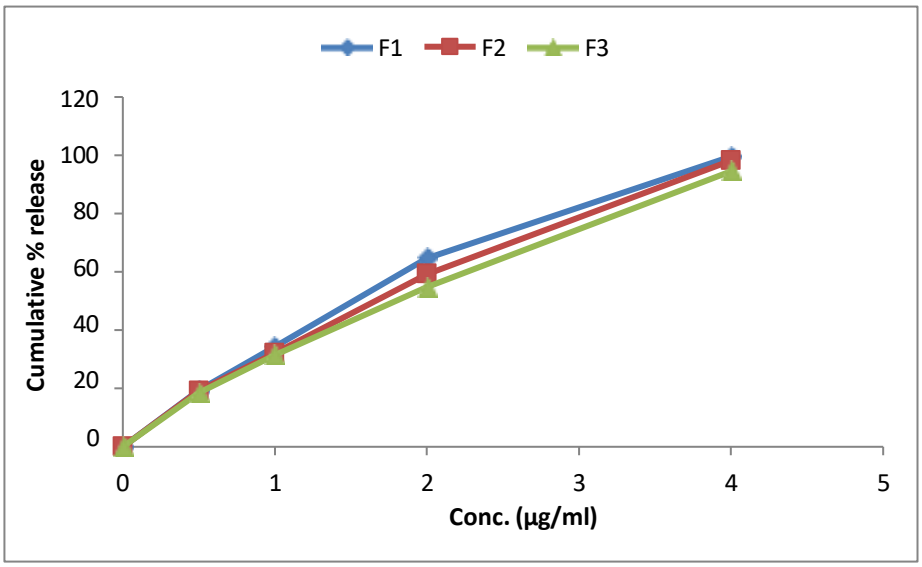


Fig 7.3 In vitro release profile of PVS from mucoadhesive buccal tablets (F4-F6)

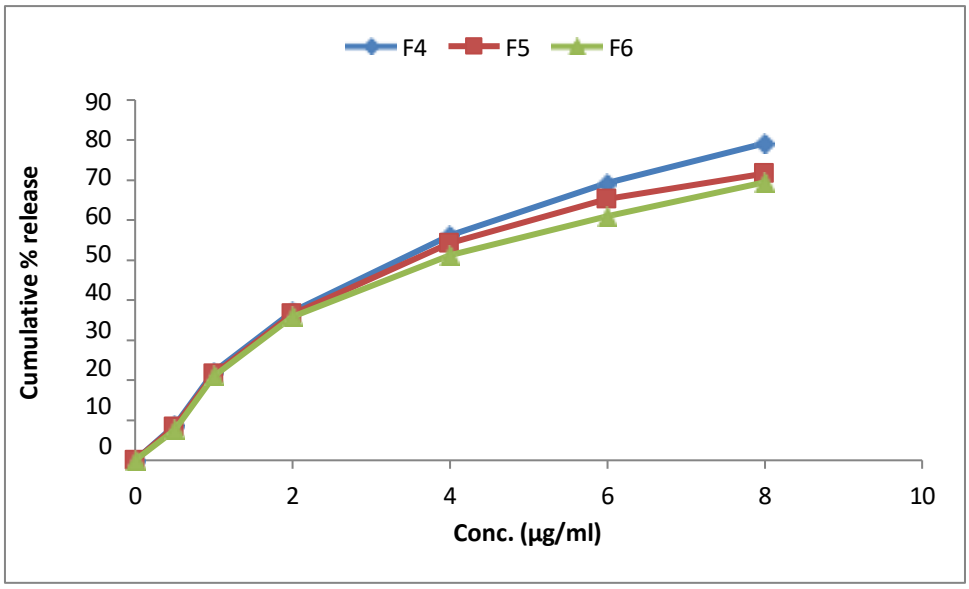
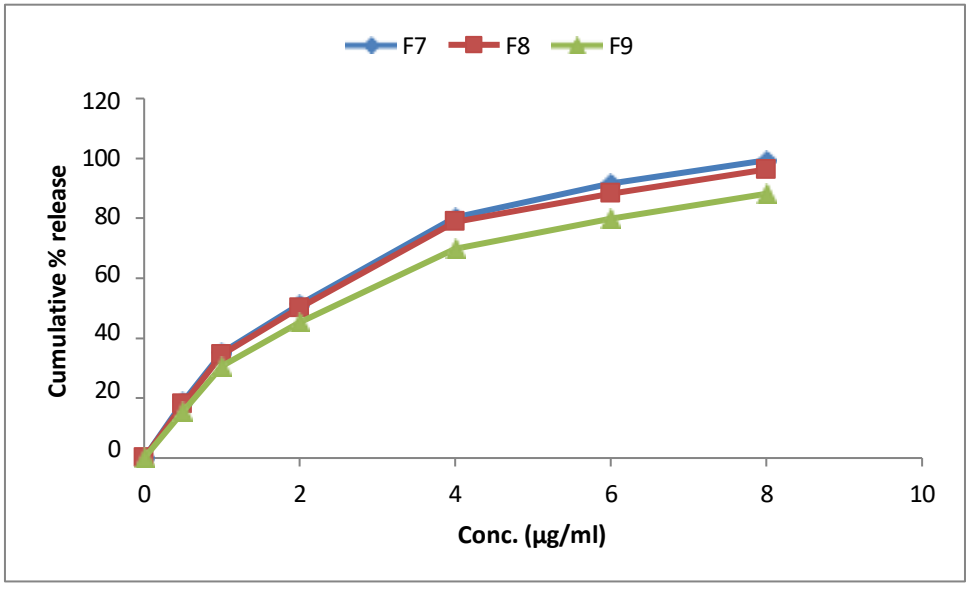


Fig 7.4 In vitro release profile of PVS from mucoadhesive b



SUMMARY AND CONCLUSION

Mucoadhesive buccal drug delivery system is a promising tool for the drugs with low oral bioavailability due to extensive first pass effect and also this route provides an easy termination of drug effect. Pravastatin presents a low bioavailability of 17% due to extensive first pass metabolism. In the present work, mucoadhesive buccal tablets of Pravastatin sodium were prepared using chitosan, HPMC K4M and xanthan gum by direct compression method.

Preformulation studies like organoleptic properties, solubility, melting point, and FTIR spectroscopy were carried out to identify and determine the purity of the drug. The calibration curve of the drug was prepared in PBS pH 6.8 at 239nm. The method obeyed Beer-Lambert's law in the steady range of 2-20 µg/ml with a high r^2 value of >0.99 and low standard deviation suggested that the method was reproducible and hence suitable for estimation of Pravastatin sodium. The compatibility study was done by mixing the drug with a various excipient and results concluded that there were no interactions observed between drug and the excipients used so that they could be used for the formulation of Pravastatin sodium buccal tablets. All the procedures were performed according to standard references.

Mucoadhesive buccal tablets of Pravastatin sodium were prepared by direct compression method using chitosan, HPMC K4M and xanthan gum as polymer. The optimized formulations of Pravastatin sodium mucoadhesive buccal tablets are presented in Table

6.1. All the prepared mucoadhesive buccal tablets of Pravastatin sodium were evaluated for thickness, hardness, friability, weight variation, uniformity of drug content, surface pH determination, swelling index, in vitro mucoadhesive strength and in vitro drug release. The results of in vitro release study were in full support of swelling study. The in vitro release of Pravastatin sodium mucoadhesive buccal tablets was in the order of, HPMC K4M < xanthan gum < chitosan.

The short term stability study was performed as per ICH guidelines using selected buccal tablets for a period of 3 months. The tablets were periodically evaluated for drug content and the results are represented in Table 7.6. The evaluated parameter did not show any

significant change during the time course of storage confirmed that the prepared buccal tablets were stable.

CONCLUSIONS

The study performed on "Formulation and evaluation of mucoadhesive buccal tablets of Pravastatin sodium" reveals following conclusion:

- The mucoadhesive buccal tablets of Pravastatin sodium could be prepared using chitosan, HPMC K4M and xanthan gum by direct compression method.
- All the prepared tablets were in acceptable range of weight variation, hardness, thickness, friability and drug content as per pharmacopoeial specification.
- The surface pH of prepared buccal tablets was in the range of salivary pH, suggested that prepared tablets could be used without risk of mucosal irritation.
- All the tablets showed good mucoadhesive strength and swelling properties.
- The in vitro release of drug was extended up to 8 h. Hence chitosan, HPMC K4M and Xanthan gum could be used to prepared prolonged released buccal tablet.
- The prepared mucoadhesive buccal tablets of were stable during testing period.

Hence, the mucoadhesive buccal tablets of Pravastatin sodium can be prepared with enhanced bioavailability and prolonged therapeutic effect.

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