IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

FORMULATION AND EVALUATION OF SIMVASTATIN BUCCAL PATCHES

Corresponding Author: **A.Vibhavari*[1],** Department of Pharmaceutics, GBN Institute of Pharmacy, Ghatkesar, Telangana ,India.

Co-authors: **Muralidhar Rao Akkaladevi[2]**, G.Vijaya Sindhur[5,] Department of Pharmaceutics, St. Mary's College of Pharmacy, Secunderabad, Telangana, India.

M.Bhargavi[3], M. Praveen kumar[4]

ABSTRACT

The work presented in this evaluates the use of buccal formulation for the enhancement of bioavailability of simvastatin. Buccal delivery of this drug bypasses the liver thereby first pass metabolism is avoided which resulted in the improved bioavailability. The feasibility of delivering simvastatin was investigated by conducting exvivo permeation studies using fresh porcine buccal mucosal membrane. Quality control tests were carried out followed by invitro release studies, moisture absorption studies, invitro residence time and evaluation of mechanical properties. Finally, a suitable formulation was selected and permeation studies of patches were conducted exvivo by using fresh porcine buccal mucosal membrane.

Key words: Buccal drug delivery, Buccal membrane, Simvastatin, Sustained drug release.

1. INTRODUCTION:

Extensive efforts have recently been focused on targeting a drug or drug delivery system in a particular region of the body for extended period of time, not only for local targeting of drugs but also for the better control of systemic drug delivery. Delivery of drugs via the absorptive mucosa in various easily accessible body cavities, like the buccal, nasal, ocular, sublingual, rectal, and vaginal mucosae, offers distinct advantages over peroral administration for systemic drug delivery. The main advantage of using these routes is that they avoid the first -pass effect of drug clearance.The buccal drug delivery is defined as the drug administration through the

mucosal membranes lining the cheeks (buccal mucosa). The main impediment to the use of many hydrophilic macromolecular drugs as potential therapeutic agents is their inadequate and erratic oral absorption. The future challenge of pharmaceutical scientists is to develop effective non-parenteral delivery of intact proteins and peptides to the systemic circulation. Based on our current understanding of biochemical and physiological aspects of absorption and metabolism of many biotechnologically- produced drugs, they cannot be delivered effectively through the conventional oral route. Because after oral administration many drugs are subjected to presystemic clearance extensive in liver, which often leads to a lack of significant correlation between membrane permeability, absorption and bioavailability *(sanders et al.,1990)*. Difficulties associated with the parenteral delivery and poor oral bioavailability provided the impetus for exploring alternative routes for the delivery of such drugs. These include routes such as pulmonary, ocular, rectal, sublingual, vaginal and transdermal. In the absence of external stimuli to facilitate the absorption, use of these alternative routes had limited success.

2. MATERIALS AND METHODS:

Table 1 :List of materials used for study

S.no	Material	Source
1	Simvaststin	Fine labs
2	HPMC E15	Qualikems Fine Chemicals pvt.Ltd
3	Dichloromethane	Finar chemicals Ltd
4	Methanol	Finar chemicals Ltd
5	Propylene glycol	Finar chemicals Ltd
6	Tween 80	Finar chemicals Ltd
7	Sodium Hydroxide	Sisco Research Laboratories pvt Ltd
8	Potassium dihydrogem ortho phosphate	Qualikems Fine chemicals pvt.Ltd
9	Phenol red	Himedia.Ltd
10	Dialysis membrane	Himedia Laboratories pvt.Ltd

METHODOLOGY:

2.1. PREFORMULATION STUDIES:

2.1.1. DETERMINATION OF ABSORPTION MAXIMA VALUES

Standard stock solution of Simvastatin (100mg/ml) was prepared in 6.8 P H Phosphate buffer. For the selection of analytical wavelength, solution of Simvastatin of concentration 20mg/ml was prepared by appropriate dilution of standard stock solution with phosphate buffer PH 6.8 and scanned in the spectrum range from 200 to 400nm. The wavelength with maximum absorption was chosen for further analysis. From the overlain spectra of the drug, wavelength 240nm was selected for analysis.

2.1.2. CONSTRUCTION OF CALIBRATION CURVE OF NICOTINE

Construction of calibration curve of nicotine in PH 6.8 & 7.4 Phosphate buffer: The stock solution was freshly prepared by dissolving 100mg of Simvastatin in 6.8P H Phosphate buffer in a 100ml volumetric flask and then making up the solution up to the mark using 6.8 P H Phosphate buffer for obtaining the solution of strength 1000µg/ml (Stock I). From this primary stock 10ml of this solution is diluted to 100ml with distilled water to obtain a solution of strength 100µg/ml (Stock-II). From this secondary stock 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0 ml were taken separately and made up to 10ml with PH 6.8 Phosphate buffer to produce 5, 10, 15, 20, 25, 30, 40 and 60 µg/ml respectively. The absorbance was measured at 240nm using a UV Visible Spectrophotometer (BIOCHROM). Similarly standard graph of Simvastatin in PH 7.4 Phosphate buffer were plotted. The standard curve of Simvaststin in 6.8 and 7.4 PH Phosphate buffers are shown in figures 2, 3 and Table 5, 6.

2.1.3. CONSTRUCTION OF CALIBRATION CURVE OF SIMVASTATIN IN WATER:

The stock solution was freshly prepared by dissolving 100mg of Simvastatin in 100ml of Water in a 100ml volumetric flask and then making up the solution up to the mark using Water for obtaining the solution of strength 1000µg/ml (Stock-I). From this primary stock 10ml of this solution is diluted to 100ml with distilled water to obtain a solution of strength 100µg/ml (Stock-II). From this secondary stock 0.5, 1.0, 1.5,

2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0 ml were taken separately and made up to 10ml with Water to produce 5, 10, 15, 20, 25, 30, 40 and 60 µg/ml respectively. The absorbance was measured at 240nm using a UV Visible Spectrophotometer (BIOCHROM). The results are shown in figure 4 and Table 7.

2.2 SATURATION SOLUBILITY STUDIES:

A Saturated solution of Simvastatin was made by adding an excess drug to 6.8 P H by adding an excess 6.8 P H Phosphate buffer and 7.4 PH Phosphate buffer. Then they were placed on a mechanical shaker for agitation for 48hrs. Then the suspension was filtered through Whatman filter paper, filtrate was collected and the drug content was estimated using UV Visible Spectrophotometer at 240 nm.

2.3 *EX VIVO* PERMEATION STUDIES THROUGH PORCINE BUCCAL MUCOSA

The aim of the study was to investigate the permeability of buccal mucosa to Simvastatin. It is based on the generally accepted Hypothesis that the epithelium is the rate limiting barrier in buccal absorption. The oral mucosa of pigs resembles that of humans more closely than any other animal in terms of structure and composition and therefore porcine buccal mucosa was selected for drug permeation studies.

2.3 (a)TISSUE PREPARATION

Buccal tissue was taken from pigs at slaughter house. It was collected within 10 minutes after slaughter of the pig and tissue was kept in Krebs buffer solution. It was transported immediately to the laboratory and was mounted within 2hrs of isolation of buccal tissue. The tissue was rinsed thoroughly using Phosphate buffer saline to remove any adherent material. The buccal membrane from the tissue was isolated and buccal epithelium was carefully separated from the underlying connecting tissue. Sufficient care was taken to prevent any damage to the buccal epithelium.

Table 2 : COMPOSITION OF TYRODE SOLUTION (KREBS BUFFER)

INGREDIENTS	QUANTITY
Sodium chloride	8.0gm
Potassium chloride	0.2gm
Calcium chloride dehydrate	0.134gm
Sodium bicarbonate	1.0gm
Sodium dihydrogen orthophosphate	0.05gm
Glucose monohydrate	1.0gm
Magnesium chloride	0.1gm
Distilled water upto	1 litre

2.3 (b) PROCEDURE

The buccal epithelium was carefully mounted in between the two compartments of a Franz diffusion cell with an internal diameter (ID) of 2 cm (4 cm2 area) and a volume of 18 ml of 7.4 pH phosphate buffer solution was placed in the receptor compartment. The donor compartment contained 5ml of 6.6 pH Phosphate buffer in which 5mg if Nicotine was dissolved. The donor compartment also contained phenol red at a concentration of 20µg/ml. This is because phenol red acts as a marker compound and is not expected to permeate through the porcine buccal membrane. Absence of phenol red in the receiver compartment indicates the intactness of the buccal membrane. The entire setup was placed over magnetic stirrer and the temperature was maintained at about 370C at 50 rpm. The samples were collected at 0.5, 1.0, 2.0, 3.0, 4.0, 6.0 hr and the amount of drug permeated through the buccal mucosa was then determined by measuring the absorbance at 260nm using a UV Spectrophotometer. All the experiments were performed in triplicate.

2.3 (c) CALCULATION OF FLUX

The cumulative amount of drug permeated, Q, per unit surface area was plotted verses time (t). In a steady state situation, the flux J, is defined as the slope of this line:

J=dQ/Adt where A is the surface area

2.4 OPTIMIZATION OF PATCHES

Bioadhesive buccal patches (Placebo) were prepared and optimized. They were optimized for polymer content, Plasticizer content and solvent volume. The patches were casted in anumbra Petri plates which provide a flat surface. The patches were checked for reproducibility of total weight of the patch, weight of the patch for fixed area and thickness of the patch**.**

2.5 FORMULATION AND PREPARATION OF PATCHES

Mucoadhesive buccal patches were prepared with HPMC E15 and formulated with different drug and polymer ratios. The patches prepared were soluble and erodible.

2.5.1. PREPARATION OF PATCHES BY SOLVENT CASTING TECHNIQUE

Weighed quantity of HPMC E15 was taken in a boiling tube. To this 20ml of solvent mixture of Dichloromethane: Methanol (1:1) was added and vortexed. Sufficient care was taken to prevent the formation of lumps and the boiling tube was set aside for 6 hrs to allow the polymer to swell. After swelling, to this mixture, measured quantity of plasticizer propylene glycol was added and vortexed. Finally weighed quantity of drug was dissolved in 5ml of solvent system and added to the polymer solution and mixed well. It was set aside for some time to remove any entrapped air and transferred into a previously cleaned anumbra Petri plate. Drying of this patch was carried out in an oven placed over a horizontal surface, with temperature beingmaintained at 40°C. The patches formed were removed carefully and stored in a dessicator till the evaluation tests were performed. The composition of the patches is given below. Formulated patches were then subjected to the weight variation test, thickness variation test and content uniformity.

Table 3: Formulation ingredients of Simvastatin buccal patches

FORMULATION	SIMVASTATIN (mg)	HPMC E15 (mg)	DCM& methanol (1:1) (ml)	Propylene Glycol(ml) 15% (w/v)
F1(1:2.5)	111	278.16	25	0.04
F2 (1:5)	111	556.32	25	0.106
F3(1:7.5)	111	834.48	25	0.160

2.6 EVALUATION TESTS

2.6.1. WEIGHT VARIATION TEST

Each formulation was prepared in triplicate and three patches each equivalent to 4cm2 were cut from each plate. Their weight was measured using shimadzu digital balance. The mean ± SD values (Table:9) were calculated for all the formulations.

2.6.2. THICKNESS VARIATION TEST

The thickness of the patches was measured at three different points of the patch by digital screw gauge (Digimatic outside micrometer, Mitutoyo, Japan). The mean ± SD values (Table:9) were calculated for all the formulations.

2.6.3. FOLDING ENDURANCE

Folding endurance of the patches were determined by repeatedly folding one patch at the same place till it broke or folded up to 200 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at Chapter VI Methodology the same place without breaking gave the value of the folding endurance of the patch. (Table: 10)

2.6.4. SURFACE PH OF THE FILMS

For determination of surface PH three films of each formulation were allowed to swell for 2hrs on the surface of an agar plate. The surface PH was measured by using PH meter, electrode was placed on the surface of the swollen patch allowing it to equilibrate for one minute. A mean of three readings was recorded. (Table: 10)

2.6.5. ASSAY OF THE PATCHES

The formulated patches were assayed for drug content in each case. Three patches from each formulation equivalent to 2cm2 area were assayed for content of drug. Each formulation was casted in triplicate and one patch from each was taken and assayed for content of drug.

2.6.5 (a)PROCEDURE:

Patches from each formulation series were taken and each patch was cut into small pieces. The pieces were taken into a 100ml of conical flask, allowed to dissolve in 100ml of PH 6.8 Phosphate buffer. The solution was filtered through 0.45 micron filter paper and diluted approximately with phosphate buffer PH 6.6 and the drug content was estimated using UVVisible Spectrophotometer (BIOCHROM, INDIA) at 260nm. (Table: 11)

2.6.6. MOISTURE ABSORPTION STUDIES

The polymers used for the formulation of mucoadhesive patches are hydrophilic polymers. The moisture absorption studies give an indication about the relative moisture absorption capacities of polymers and an idea whether the formulation maintains its integrity after absorption of moisture. 5% w/v agar in distilled water, in hot condition, was transferred into Petri plates and it was allowed to solidify. Six drug free patches of each formulation were selected and weighed. They were placed in desiccator overnight prior to the study to remove moisture if any and laminated on one side with water impermeable backing membrane. They were placed on the surface of the agar and incubated at 370C for one hour in incubator. The patches were removed and weighed again. The percentage of moisture absorbed can be calculated using the formula

$$\% \text{ Moisture absorbed} = \frac{\text{Final weight-Initial weight} \times 100}{\text{Initial weight}}$$

2.6.7. MEASUREMENT OF MECHANICAL PROPERTIES

Mechanical properties of the films (patches) were evaluated using a microprocessor based advanced force gauze equipped with a motorized test stand (Ultra Test, Mecmesin, West Sussex, UK), equipped with a 25 kg load cell. Film strip with the dimensions 60 x 10 mm and free from air bubbles or physical imperfections, were held between two clamps positioned at a distance of 3 cm. A cardboard was attached on the surface of the clamp to prevent film from being cut the grooves of the clamp. During measurement, the strips were pulled by the top clamp at a rate of 2.0 mm/s to a distance till the film broke. The force and elongation were measured when the films were broken. Results from film samples, which were broken at end and not between the clamps were not included in observations. Measurements were run in six replicates for each formulation. The following equations were used to calculate the mechanical properties of the films.

$$\text{Tensile strength (kg.mm-2)} = \frac{\text{Force at break(kg)}}{\text{Initial cross sectional area of the sample (mm2)}}$$

$$\text{Elongation at break(\%mm-2)} = \frac{\text{Increase in length(mm)}}{\text{Original length}} \times \frac{100}{\text{Cross sectional area (mm2)}}$$

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2.6.8. *IN VITRO* BIOADHESIVE STRENGTH

The bioadhesive strength of the buccal patches was determined using an ultra-test (Mecmesin, west Sussex UK) equipped with a 5-kg load cell. The fresh porcine buccal mucosa obtained from slaughterhouse was stored in simulated saliva solution (2.38 g Na2HPO4, 0.19 g KH2PO4 and 8.00 g Nacl in 1000 ml of distilled water at PH 6.75). The porcine buccal mucosa was secured tightly to a circular stainless-steel adapter of a diameter 2.2 cm provided with the equipment. This was fixed to advanced force gauze. The buccal patch to be tested was placed over another cylindrical stainless-steel adaptor of similar diameter and mounted on the platform of motorized test stand. Buccal patch with a backing membrane was adhered on to it using a solution of cycnoacrylate adhesive. All measurements were conducted at room temperature. During Measurement 100µl of 1% mucin solution of crude mucin procured from sigma chemicals was used to moisten the porcine buccal membrane. The upper support was lowered at a speed of 0.5 mm/s until contact was made with the tissue at the predetermined force of 0.5 N for a contact time of 180 sec. At the end of the contact time upper support was withdrawn at a speed of 0.5mm/s to detach the membrane from the patch. Data collection and calculations were performed using the data plot software package of the instrument. Two parameters, namely the work of adhesion and peak detachment force were used to study the buccal adhesiveness of patches (Vamshi *et al*., 2007). The work of adhesion was determined from the area under force distance curve while the peak detachment force required detaching from tissue.

2.6.9. *IN VITRO* RELEASE STUDIES

The *in vitro* drug release studies were performed by using USP Type II dissolutionChapter VI test apparatus (paddle method). Patches of desired size were cut and since the patches were meant to release the drug from only one side, therefore an impermeable backing membrane was placed on one side of the patch. A film of 4cm2 size was cut and attached to a glass slide with a solution of cyanoacrylate adhesive. This slide was kept at an angle of 45º in a 1000 ml beaker containing 500 ml of phosphate buffer of pH 6.6. The dissolution medium was maintained at a temperature of 37 ± 0.5º C and stirred at 50 rpm. At predetermined time intervals samples were withdrawn and replaced with fresh dissolution medium. Absorbance was measured using UV- VISIBLE spectrophotometer. Drug release, cumulative percentage of drug released and standard deviation were calculated and the results were presented in Table 4

Table 4 : Parameters used for the dissolution study

Apparatus	**USP Dissolution apparatus (Type II)**
Dissolution medium	Phosphate buffer (pH 6.6)
Temperature	37 + 0.5 °C
Volume	500 ml
Speed	50 rpm
Sample withdrawn	5 ml
Running Time	6hr

2.6.9 (a): RELEASE KINETICS

Data of in vitro release was fit into different equations to explain the release kinetics of Nicotine release from buccal patches. The kinetic equations used were Zero order and First order equations.

A) Zero order release kinetics:

It defines a linear relationship between the fractions of drug released at a time t.

$$Q = Kt$$

Where Q-Fraction of drug released at time t ,*K* - is the zero-order rate constant expressed in units of concentration/time ,t -is the time in hrs.

B) First order release kinetics

This model is been used to describe absorption and /or elimination of some drugs. The release of the drug which followed first order kinetics can be expressed by the equation

$$Log\ C = LogC0 - Kt / 2.303$$

Where, *C0* - is the initial concentration of drug, *K* - is the first order constant ,*t* - is the time in hrs.

The data obtained are plotted as log cumulative % of drug remaining versus time which

would yield a straight line with a slope of $-K/2.303$

2.6.9 (b): MODELS OF DRUG RELEASE MECHANISM

The release data of buccal patches was fitted into different mechanism models like Higuchi model, Korsemeyer- Peppas model, Hixson Crowell model.

A) Higuchi (Diffusion) Equation: It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$$Qt = Kt\ 1/2$$

Where, *Qt* - is the amount of the release drug in time t, *K*- is the kinetic constant t- is time in hrs .

A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the ficks law, square root time dependent.

B)Korsmeyer Peppas kinetics: A plot of the fraction of logarithm of % drug released against logarithm of the time will be linear if the release obeys Korsmeyer Peppas equation.

$$Mt/M\infty = Kt\ n$$

Where *Mt* - represents amount of the released drug at time t, *M*∞- is the overall amount of the drug (whole dose) released after 12 hrs ,Mt/ M∞-Fraction of drug released at time t. K- is the diffusional characteristic of drug/ polymer system constant n- is a diffusional exponent that characterizes the mechanism of release of drug.

C) Hixon –crowell (Erosion) model: This equation defines the drug release based on formulation erosion alone

$$Q=1-(1-Kt)3$$

where, Q- Fraction of drug released at time K-Release rate constant Thus a plot between (1-Q)1/3 against time will be linear if the release obeys erosion equation.

2.6.10. *EX VIVO* PERMEATION OF SIMVASTATIN PATCHES THROUGH PORCINE BUCCAL MUCOSA

Ex vivo permeation of Simvastatin from buccal patches through porcine buccal membrane was studied. Porcine buccal mucosa was obtained and buccal membrane was isolated. The membrane was mounted over a Franz diffusion cell and a buccal patch was placed over the membrane. A dialysis membrane was placed over the membrane so as to secure the patch tightly from getting dislodged from the membrane (the buccal patch was sandwiched between the buccal mucosa and the dialysis membrane). The receptor compartment of diffusion cell contained Phosphate buffer of 7.4 PH . The setup was placed over a magnetic stirrer with temperature maintained at 37^0C. Samples were withdrawn and replenished immediately from the receiver compartment at 0.5, 1, 2, 3, 4, 6 hr. They were stored underrefrigerated conditions till the analysis was carried out. The content of Simvastatin in the samples was analyzed by UV-Visible Spectrophotometer at the wavelength of 260 nm. All the experiments were performed in triplicates.

Fig 1: Diffusion Apparatus for *Ex vivo* permeation study

3. RESULTS AND DISCUSSION

3.1 Preformulation study:

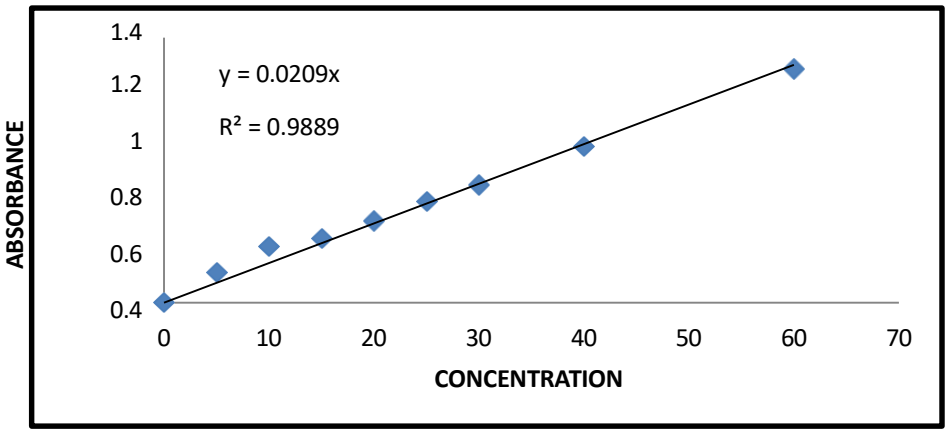
3.1.1. STANDARD GRAPH OF SIMVASTATIN IN PHOSPHATE BUFFER PH 6.8(λ max 240nm)

Standard graph of Simvastatin was plotted as per the procedure in experimental method andits linearity is shown in the Table 14. The standard graph of Simvastatin Showed good linearity with R2 of 0.988, which indicates that it obeys “Beer-Lamberts” law.

Table 5 : Standard graph of Simvastatin in phosphate buffer PH 6.8

CONCENTRATION (µg/ ml)	ABSORBANCE
0	**0**
5	0.162
10	0.296
15	0.342
20	0.432
25	0.534
30	0.621
40	0.825
60	1.234

Fig 2: standard graph of simvastatin in phosphate buffer p^{h} 6.8



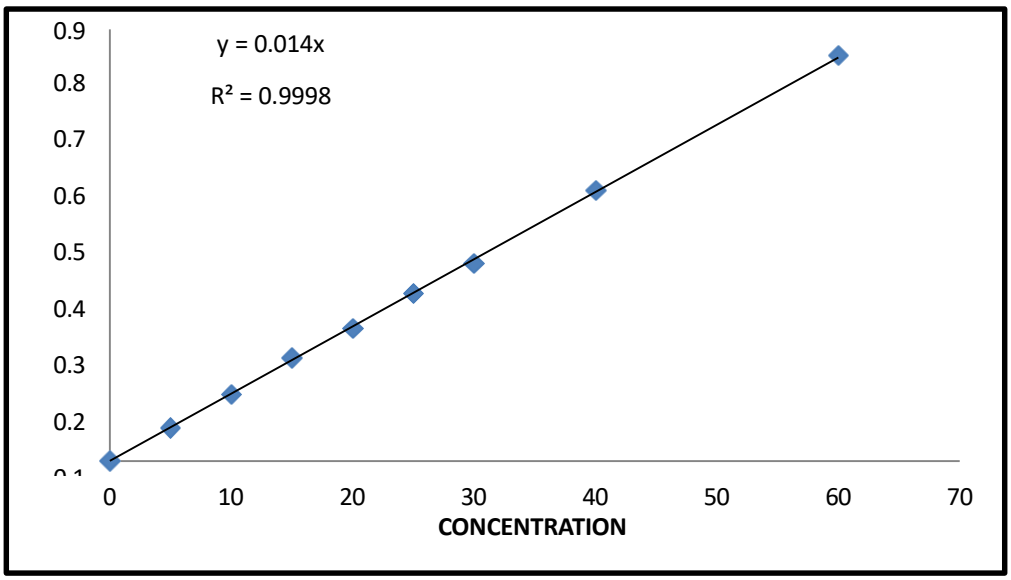
3.1.2. STANDARD GRAPH OF SIMVASTATIN IN PHOSPHATE BUFFER P H 7.4(λ max 240nm)

Standard graph of Simvastatin was plotted as per the procedure in experimental method and its linearity is shown in the Table 15.The standard graph of Simvastatin Showed good linearity with R2 of 0.988, which indicates that it obeys "Beer-Lamberts" law.

Table 6 :Standard graph of Simvastatin in phosphate buffer PH 7.4

CONCENTRATION (µg/ mL)	ABSORBANCE
0	0
5	0.069
10	0.139
15	0.215
20	0.277
25	0.349
30	0.413
40	0.564
60	0.846

Fig .3 STANDARD GRAPH OF SIMVASTATIN IN PHOSPHATE BUFFER PH 7.4



3.1.3. STANDARD GRAPH OF SIMVASTATIN IN WATER

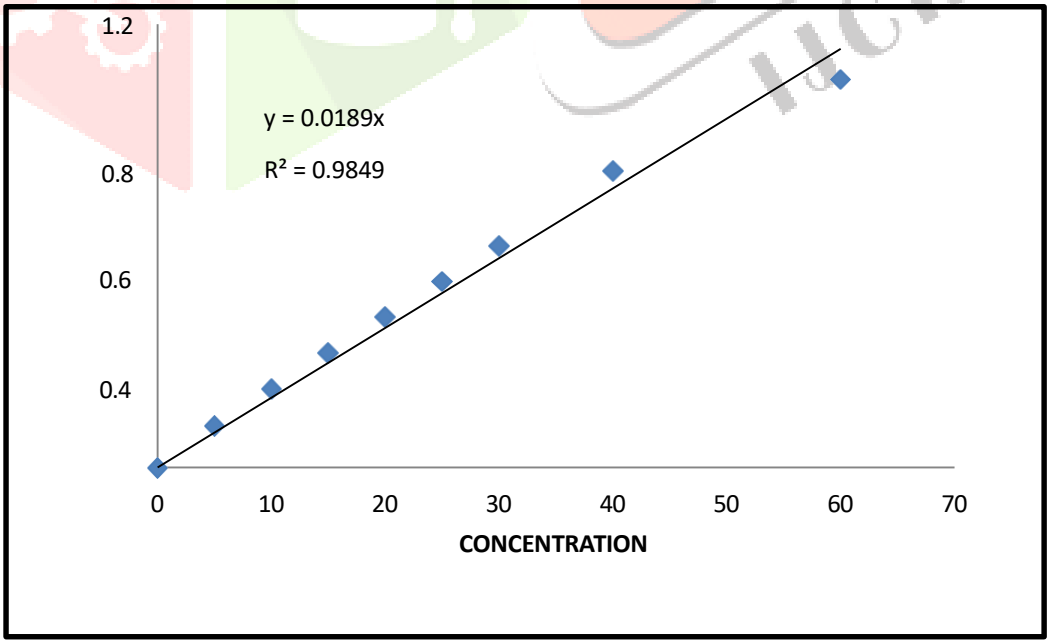
(λ max 240nm)

Standard graph of Simvastatin was plotted as per the procedure in experimental method and its linearity is shown in the Table 16.The standard graph of Simvastatin Showed linearity with R2 of 0.984, which indicates that it obeys “Beer-Lamberts” law.

Table 7:Standard graph of Simvastatin in water

CONCENTRATION (µg/ mL)	ABSORBANCE
0	0
5	0.114
10	0.213
15	0.312
20	0.408
25	0.505
30	0.601
40	0.804
60	1.052

Fig 4: STANDARD GRAPH OF SIMVASTATIN IN WATER



In-vivo permeation of Simvastatin drug solution through Whatman filter paper

In-vivo Permeation study of Drug solution through the whatman filter paper was performed using Franz diffusion cell. The membrane assembly was kept at 37±0.2^{0}C. This was maintained by magnetic stirrer. Phenol red was used as marker compound to permeate through filter paper.

Table 8

Time(hrs)	Cumulative percentage permeated
0	0
0.5	36.51
1	45.36
2	50.40
3	62.02
4	66.34
6	71.79
FLUX	0.23µg /hr/cm^2

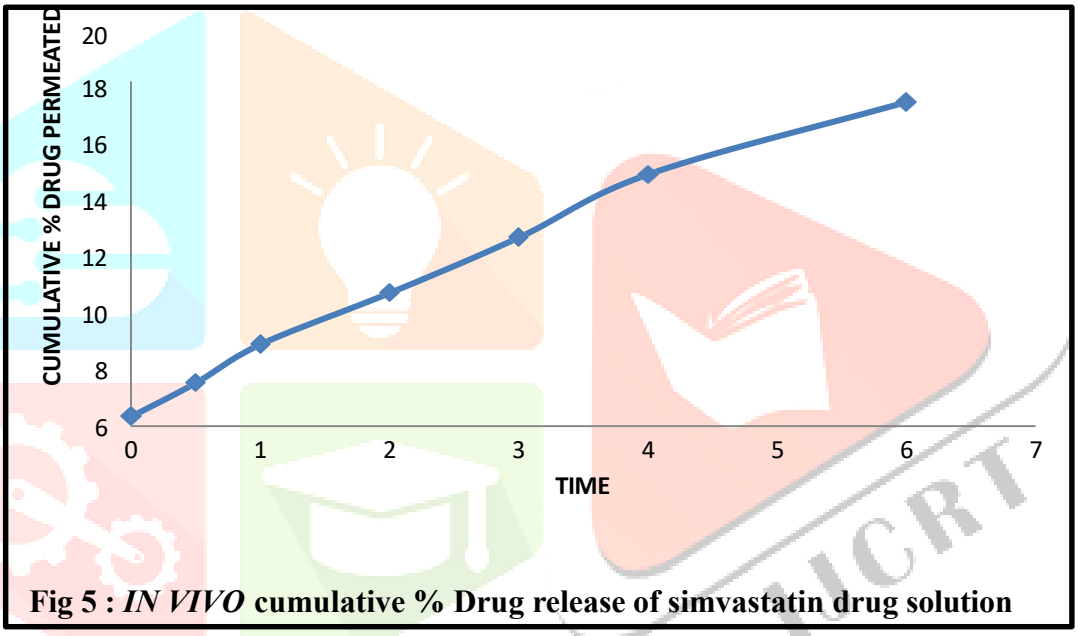


Fig 5 : *IN VIVO* cumulative % Drug release of simvastatin drug solution

Table 9

WEIGHT VARIATION AND THICKNESS VARIATION OF PATCHES

S.No	FORMULATION CODE	WEIGHT(mg)	THICKNESS (mm)
		MEAN ±SD	MEAN ±SD
01	F1	16.2±0.98	0.53±0.20
02	F2	40.3±0.60	0.11±0.01
03	F3	49.5±0.75	0.13±0.01

Each value represents the mean ±SD (n=3)

The prepared patches were smooth in appearance and no visible cracks .The weight of patches ranged from 15.2±0.98 to 48.5±0.75mg and the thickness ranged from 0.53±0.20 to 0.13±0.01.

Table 10

SURFACE P^H & FOLDING ENDURANCE OF SELECTED SIMVASTATIN BUCCAL PATCHES

S.No	FORMULATION CODE	SURFACE pH	FOLDING ENDURANCE
		MEAN ±SD	
01	F1	6.27±0.22	>100
02	F2	6.9±0.08	>100
03	F3	6.64±0.82	>100

Each value represents the mean ±SD (n=3)

The surface p^H of all the films found to be near to the buccal p^H, hence they do not cause any irritation and Folding Endurance was found to be >100.

Table 11

ASSAY OF SIMVASTATIN BUCCAL PATCHES

S.No	FORMULATION CODE	ASSAY(%)
		MEAN ±SD
01	F1	97.6±0.57
02	F2	98.4±0.55
03	F3	99.4±0.25

Each value represents the mean ±SD (n=3)

The drug content estimation showed values in the range of 97.6±0.57 to 99.4±0.25 which reflects good uniformity in the drug content among different formulations.

Table 12

MOISTURE ABSORPTION STUDIES

S.No	FORMULATION CODE	%MOISTURE ABSORBED
		MEAN ±SD
01	F1	35.17±1.24
02	F2	40.14±8.99
03	F3	45.13±3.72

Each value represents the mean ±SD (n=3)

The moisture absorption studies gave an indication of the relative moisture absorption capacities of polymers and the integrity of the formulations. Moisture absorption studies were found to be in the range of 35.17±1.24 to 45.13±3.72.

Table 13

MECHANICAL PROPERTIES OF SIMVASTATIN BUCCAL PATCHES

S.No	FORMULATION CODE	TENSILE STRENGTH (Kg/mm^2)	ELONGATION AT BREAK ($\%mm^{-2}$)
		MEAN ±SD	MEAN ±SD
01	F1	3.1±0.248	13.98±0.08
02	F2	2.87±0.826	13.56±0.61
03	F3	3.76±0.612	14.21±0.02

Each value represents the mean ±SD (n=3)

Ideal buccal patch, apart from good bioadhesive strength, should be flexible, elastic and strong enough to withstand breakage due to stress caused during its residence in the mouth. Formulation F3 showed tensile strength of 3.76 and Elongation at break showed 14.21 mm^{-2}.

***IN VITRO* DRUG RELEASE STUDIES**

The invitro drug release profiles of Simvastatin from buccal patches are shown in the table 23 and figure 13. In case of formulation F1 containing HPMC E15 alone in the ratio of 1:2.5 (Drug:polymer) showed about 87.48±0.85% of drug release in 6 hrs. This is because the polymer HPMC E15 used was a low viscosity polymer and unlike other grades of polymer like HPMC K4M, K15 or K100M, HPMC E15 dissolves much faster and drug was diffused from the patches onto the surface.

In case of formulations F2, F3 initially the drug release was rapid more than 50% released in 3hrs and followed by slow release 71±0.71% and 74.15±1.15% in 6 hrs. There appeared no significant difference in the final percentage of drug release, which is due to the fact that in all the formulations the drug dissolved completely in the dissolution medium. It is clear from the plots that the drug release was governed by polymer content. No lag time was observed as the patch was directly exposed to the dissolution medium. An increase in

the polymer content was associated with decrease in drug release rates. This is because increasing the amount of polymer in the patches, forms a water swollen gel like state that could substantially reduce the penetration of dissolution medium into the patches and so the drug release was retarded. The formulation F3 was selected as optimized formulation based on these invitro release studies which showed satisfactory drug release rates 74.15±1.15% in 6hrs.

Table 14

***IN-VITRO* PERCENTAGE DRUG RELEASE PROFILES OF SIMVASTATIN FORMULATIONS WITH HPMC E15**

Time(hrs)	Percentage Drug Release		
	F1	F2	F3
	MEAN ±SD	MEAN ±SD	MEAN ±SD
0.5	19.47±2.32	31.1±0.83	39.3±0.31
1	37.64±1.22	53.98±0.96	46.12±1.05
2	54.32± 1.05	57.41±0.55	51.25±0.68
3	71.75±2.52	61.51±0.71	58.05±0.57
4	79.97±1.45	63.9±1.35	64.57±0.39
6	87.48±0.85	71.71±0.71	74.15±1.15

Each value represents the mean ±SD (n=3)

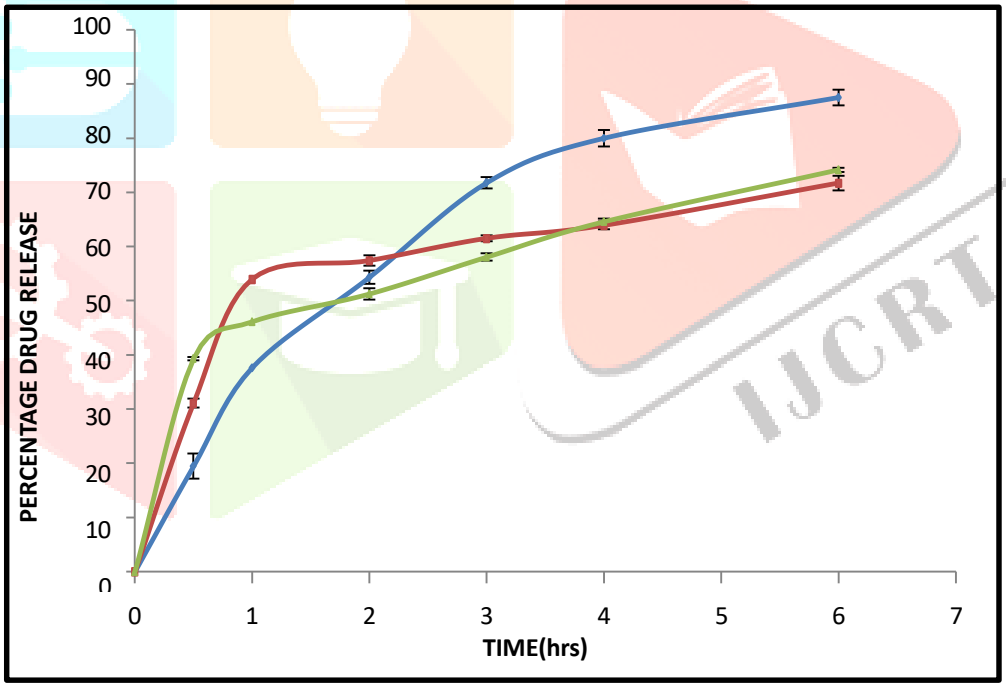


Fig 6 :Cumulative % drug release profiles of different formulations

SUMMARY AND CONCLUSIONS

The work presented in the manuscript evaluates the use of buccal formulation for the enhancement of bioavailability of Simvastatin. Buccal delivery of this drug bypasses the liver , thereby first-pass metabolism is avoided which resulted in the improvement of bioavailability.

The feasibility of delivering Simvastatin was investigated by conducting *in vivo* permeation studies using whatman filter paper. Quality control tests were carried out followed by *in vitro* release studies, moisture absorption studies, *in vitro* residence time and evaluation of mechanical

properties. Finally, a suitable formulation was selected and permeation studies of patches were conducted *ex vivo* by using fresh porcine buccal mucosal membrane.

The following conclusions could be drawn from the results of various experiments

- Simvastatin could permeate through porcine buccal membrane as evidenced from the results of *in vivo* drug permeation studies.
- The Buccal patches were formulated by the solvent casting method with mucoadhesive polymer HPMC E15 which is soluble in both water as well as organic solvents.
- The physicochemical properties of all formulations were shown to be within the limits.
- The surface P^H of all the formulations was in an acceptable salivary P^H (5.8-7.4). Hence, they do not cause any irritation to the buccal cavity.
- *In vitro* release studies demonstrate the suitability of developed formulations for the release of Simvastatin. Satisfactory drug release rates and final percentage of drug release could be obtained from the selected formulations.
- Buccal patches had shown good mechanical properties measured in terms of tensile strength and elongation at break values may be produced with HPMC E15.
- Lower concentrations of HPMC may not be suitable for the development of buccal formulations, as they tend to lose their structure immediately and higher concentrations of HPMC may not release drug rapidly.Buccal patches developed for Simvastatin possess reasonable Bioadhesion measured in terms of peak detachment force and work of adhesion.
- The optimized formulation F3 followed first order release kinetics. The present study concludes that buccal delivery of Simvastatin patches formulated by using the polymer HPMC E15 can be a good way to bypass the first pass metabolism and to prolong the duration of action of drug by reducing the frequency of dosing of Simvastatin. Finally the present study concludes that buccal drug delivery system may be a suitable method for Simvastatin administration.

Aknowledgement:

We express our sincere thanks to our Principal and HOD Dr.**E.HARI KRISHNA**, M.Pharm., Ph.D., Principal, G.B.N Institute of Pharmacy, for granting us the opportunity to provide necessary facilities in pharmacy at this esteemed institution. Sincere thanks to Principal**Dr. Muralidhar Rao Akkaladevi** and management of St.Mary's college of Pharmacy, Secunderabad, India for providing necessary facilities throughout this study.

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