FORMULATION AND EVALUATION OF ROSUVASTATIN BUCCAL PATCHES

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***ABSTRACT :** Rosuvastatin is an antilipidemic agent that competitively inhibits hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. Like remaining statins, Rosuvastatin-calcium is also a poorly soluble drug and does not exceed 20% of bioavailability due to first-pass metabolism. To overcome these drawbacks the present study aimed to formulate a transdermal patch of Rosuvastatin calcium. Five patches were developed by incorporating HPMCk 100 and PVP K40 using the solvent casting method. The formulations were evaluated for hardness, compatibility studies, solubility, weight variation, thickness, physical appearance, tensile strength, percentage drug content, percentage moisture content, percentage moisture uptake, and in vitro drug release. The evaluated parameters were within the limit only. FTIR spectroscopy revealed that the drug, polymers, and other excipients were compatible with each other. When compared to other formulations F2 formulation exhibited a better in vitro drug release profile across the cellulose membrane. The buccal film loaded with Rosuvastatin-calcium was used conveniently as an antilipidemic agent.*

***Key Words:** Rosuvastatin, HPMCk 100, PVP K40, solvent casting method, in vitro drug release, Stability studies.*

I. INTRODUCTION

Among the various routes of drug delivery, transmucosal drug delivery offer distinct advantages over peroral administration for systemic effect. Among various transmucosal routes, buccal mucosa is the most suited for local, as well as systemic delivery of drugs[1]. The use of the oral cavity membranes as sites of drug administration has been the topic of increasing interest for the past decade. It is well known that the absorption of therapeutic compounds from the oral mucosa provides a direct entry of the drug into the systemic circulation, thereby avoiding first-pass hepatic metabolism and gastrointestinal drug degradation, both of which are associated with peroral administration[2]. Buccal films are the most recently developed dosage form for buccal administration. They have gained importance as efficacious and novel drug delivery systems and are cost-effective with good patient compliance. As buccal films are implied for attachment to the buccal mucosa, they can be formulated to exhibit local as well as systemic action[3]. The buccal film may be preferred over a buccal tablet, in terms of flexibility and comfort. Buccal films have direct access to the systemic circulation through the internal jugular vein, which bypasses the drug from the hepatic first-pass metabolism leading to high bioavailability[4]. The present study is To Formulate and Evaluation of Rosuvastatin Buccal Patches. The formulation was developed to disintegrate with immunity and ultimately provides good bioavailability and quick onset. Rosuvastatin is used along with a proper diet to help lower "bad" cholesterol and fats (such as LDL, triglycerides) and raise "good" cholesterol (HDL) in the blood. It belongs to a group of drugs known as "statins." It works by reducing the amount of cholesterol made by the liver [5,6].

II. MATERIALS

Rosuvastatin was collected as a gift sample from Hetero labs, Hyderabad, and various excipients like HPMC k, PVP K 30, Methanol, Polyethylene glycol, DMSO were purchased from AR chemicals, Hyderabad.

III. METHODOLOGY

Drug- excipient compatibility study

The compatibility of drug and formulation components is an important prerequisite for formulation development. It is therefore necessary to confirm that the drug does not interact with excipients under experimental conditions and affect the shelf life of the product or any other unwanted effects on the formulation[6].

Method

Compatibility studies were conducted to investigate and predict physicochemical interaction between drug substance and excipients and therefore to select the suitability of chemically compatible excipients. Compatibility studies were performed by preparing compatibility blends at different ratios of different excipients with drugs based on tentative average weight. These blends were stored at accelerated conditions at 40^0c, 75%RH for one

month. The control samples were stored at 40c the ratio of drug and excipient varies from 11 to 110 depending on the purpose of use and samples were kept in double-lined poly bags. the samples were evaluated for any change in physical characteristics. Samples were evaluated for any change in physical characteristics concerning the controlled sample stored at 4oc for 30 days. Taken out at two weeks intervals and were subjected to physical and chemical testing and results were noted. Chemical compatibility is tested by FTIR spectrometry, which is the most powerful technique to identify functional groups of the drug[7].

Formulation Development

Table-: 1 Formulation Design of Rosuvastatin buccal Patches

S. No	F.Code	Drug (mg)	HPMCk 100	PVP K40	PEG	DMSO
1	F1	20	40	-	1ml	0.1ml
2	F2	20	80	-	1ml	0.1ml
3	F3	20	-	40	1ml	0.1ml
4	F4	20	-	80	1ml	0.1ml
5	F5	20	40	40	1ml	0.1ml

Solvent casting method

Rosuvastatin buccal film was formulated by the solvent casting evaporation technique. The drug Rosuvastatin was diffuse in methanol. Polymers Hpmc K100 and Pvp K 40 were taken in a boiling tube, to this add Rosuvastatin drug which was previously dissolved in methanol. Sufficient care was taken to prevent the creation of lumps. PEG was taken as a plasticizer and Dimethyl sulfoxide as permeation enhancer and added to the mixture and mixed well. It was set aside for 2 hours to exclude any entrapped air and was then transferred into a previously cleaned Petri plate ($40cm^2$), drying of patches was carried out in a vacuum oven at room temperature. Dried patches were packed in aluminum foil and stored in a desiccator for further evaluation[8].

Characterization of Buccal formulation

Physicochemical evaluation

Physical appearance

All the formulated Rosuvastatin films were observed for color, clarity, flexibility, and smoothness.

Folding endurance

Buccal patches folding endurance was estimated by frequently doubling over at the same place till it broke. The number of times the film could be folded at the same place without breaking is the folding endurance. This was restated on all the films three times and the mean values plus standard deviation were calculated[9].

The thickness of the film

The thickness of each film was measured by using screw gauze. Buccal patches thickness was estimated at various sites on each patch and the average thickness of the Buccal patch was captured as the thickness of the patch[10].

Weight uniformity

The formulated Buccal patches are to be dried at 60^0C for 6 hours before trial. An identified area of 4.52 cm^2 of the film is to be cut in different parts of the patch and weighed in the digital balance. The average weight and standard deviation values are to be calculated from the individual weights[11].

Drug content

The formulated Buccal patch was assayed for drug content in each case. Three patches from each formulation were assayed for the content of the drug. Each formulation was cast in triplicate and one patch from each was taken and assayed for the content of the drug. The Buccal films (4.52 cm^2) were added to the conical flask containing 100 ml of phosphate buffer pH 7.4 containing 0.5% SLS. This was then stirred with a magnetic bead at 400 rpm for 2 hrs. The contents were filtered and the filtrate was analyzed spectrophotometrically. Similarly, a blank was prepared from Buccal films without drug[12].

Moisture absorption studies

The buccal patches were weighed exactly and placed in a desiccator containing aluminum chloride to maintain 79.50% RH. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated using the following formula[13].

$$\text{Percentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture loss studies

Three patches were weighed separately and kept in a desiccator containing calcium chloride at 37^0C for 24 hours. Then the last weight was noted when there was no further change in the weight of the patch. The percentage of moisture loss was calculated using the following formula[14].

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

***In vitro* release study:**

The release rate of the drug was determined by using Franz diffusion cell apparatus temperature maintained at 37 ± 0.5 ^{0}C and stirred at a rate of 200 rpm. Sink conditions were maintained all over the study. The vessel contained 10ml of phosphate buffer pH 6.8 phosphate buffer solution. Aliquots of 1ml of samples were withdrawn at various times meanwhile and then analyzed using a UV Spectrophotometer[15].
The % release rate of the drug was determined using the following formula.

$$\text{Percentage drug release} = \frac{Da}{Dt} \times 100$$

Where, Dt = Total amount of the drug in the film
Da = The amount of drug released

Drug release kinetics

To describe the Drug release kinetics from individual formulations, the corresponding dissolution data were fitted in various kinetic dissolution models[16]:

Zero-order, first-order, and Higuchi respectively.

$$Qt = Q0 + K0\ t \text{……..} (3)$$

where, Qt is the amount of drug released at time t; Q0 is the amount of drug in the solution at t = 0, (usually, Q0 = 0), and K0 is the zero-order release constant.

$$\log Qt = \log Q\alpha + (K1 / 2.303)\ t \text{……..} (4)$$

Qα is the total amount of drug in the matrix and K1 is the first-order kinetic constant.

$$Qt = KH.\ t^{1/2} \quad \text{(5)}$$

where,

KH is the Higuchi rate constant.

Further, to better characterize the mechanism of drug release from matrices, dissolution data were analyzed using the equation proposed by Korsmeyer and Peppas.

$$Q\ (t-l)\ /Q\alpha = KK\ (t-l)n \quad \text{(6)}$$

where Qt corresponds to the amount of drug released in time t, *l* is the lag time (*l* = 2 hours), Qα is the total amount of drug that must be released at infinite time, KK a constant comprising the structural and geometric characteristics of the tablet, and n is the release exponent indicating the type of drug release mechanism. To the determination of the exponent n, the points in the release curves where Q (t-*l*)/Qα>0.6, were only used. If n approaches 0.5, the release mechanism can be Fickian. If n approaches 1, the release mechanism can be zero-order and on the other hand if 0.5<n<1, non-Fickian (anomalous) transport could be obtained. Anomalous (non-Fickian) transport generally refers to the drug release by the summation of both diffusion and erosion of the polymeric matrix. The criteria employed to select the ‘‘best model’’ was the one with the highest coefficient of determination (r^2)[17].

Stability studies

Optimized medicated buccal films were subjected to short-term stability testing. The Buccal films were sealed in aluminum foils and kept in a humidity chamber maintained at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months as per ICH guidelines[18].

IV. RESULTS AND DISCUSSIONS

Drug - excipient compatibility studies (FT-IR)

The compatibility between the drug and the selected polymers and other excipients was evaluated using the FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-polymer mixture, which confirmed the absence of any chemical interaction between the drug, polymer, and other chemicals.

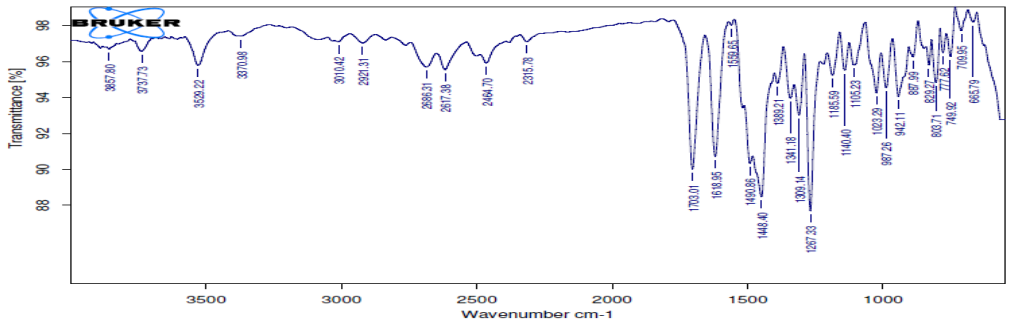

Fig.1. FT-IR Sample for Rosuvastatin

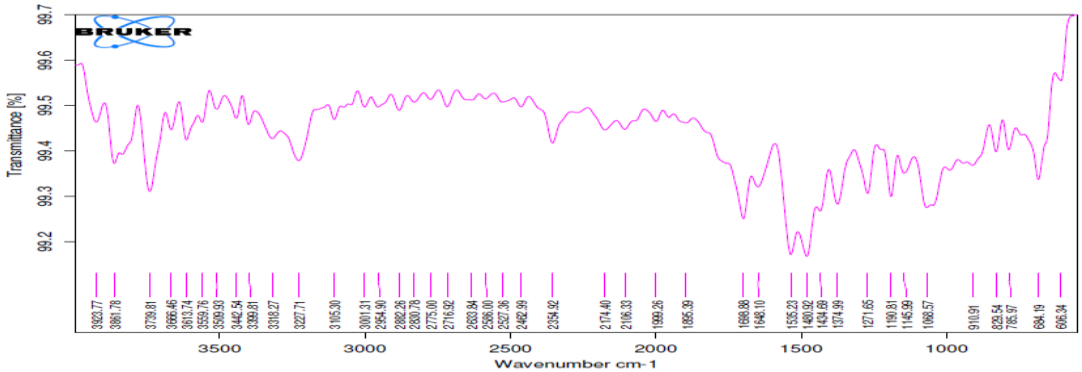

Fig.2. FT-IR Sample for drug and polymer mixture

Physical appearance and surface texture of buccal patches

These parameters were checked simply with a visual inspection of patches and by feel or touch. The observation reveals that the patches are having smooth surfaces and they are elegant.

Weight uniformity of buccal patches

The weight of the patches was determined using digital balance and the average weight of all patches

The thickness of buccal patches

The thickness of the patches was measured using a screw gauge and the average thickness of all patches.

Folding endurance of buccal patches

The folding endurance gives the idea of the flexible nature of patches. The folding endurance was measured manually, patches were folded repeatedly till they broke, and it was considered as the endpoint. The folding endurance was found optimum and the patches exhibited good physical and mechanical properties and the average folding endurance of all patches.

Drug content uniformity of buccal patches

Rosuvastatin buccal patches prepared with various polymers were subjected to the valuation for uniform dispersion of drugs throughout the patch. In each case, three patches were used and the average drug content was calculated.

% Moisture loss

The moisture content in the buccal patches ranged from 8.75 to 8.96%. The moisture content in the formulations was found to be increased by an increase in the concentration of polymers.

%Moisture absorption

The moisture absorption in the buccal patches ranged from 9.92 to 10.52%.

Swelling index

The swelling index in the buccal patches ranged from 14.58 to 15.98 %.

Table -: 2 Physicochemical evaluation data of Rosuvastatin Buccal Patches

F. code	F1	F2	F3	F4	F5
Thickness (mm)	0.31	0.29	0.28	0.26	0.3
Weight variation (mg)	45.36	48.21	50.16	49.62	48.23
Drug content Uniformity	92.26	97.41	90.84	88.82	89.69
Folding endurance	77	76	79	78	77
% Moisture loss	8.96	8.78	8.9	8.75	8.96
%Moisture absorption	10.26	10.52	9.92	10.23	10.26
Swelling index	15.98	15.85	14.58	15.25	15.98

Drug release studies

Table-: 3 *In vitro* release data of film F_1 to F_5

Time (hrs.)	F_1	F_2	F_3	F_4	F_5
0	0	0	0	0	0
1	14.90	14.15	12.80	15.56	11.25
2	26.70	25.89	26.50	25.55	27.45
3	37.89	36.87	37.70	38.25	35.12
4	48.18	45.23	44.50	47.59	47.16

5	69.75	68.35	67.65	66.55	59.82
6	76.89	70.34	71.98	75.32	74.23
7	88.86	86.77	85.32	80.28	87.90
8	94.45	96.50	90.12	89.22	92.45

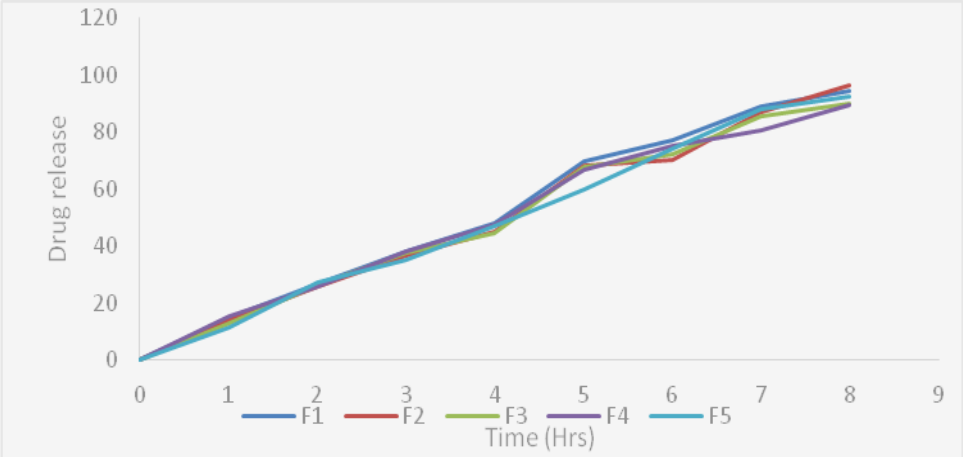

Fig.3. In vitro drug release of (F1- F5) formulation

Drug release kinetics

All the five formulations of prepared Rosuvastatin buccal patches were subjected to in vitro release studies these studies were carried out using Franz diffusion cell apparatus.

The dissolution medium consisted of 10 ml of Standard buffer pH 6.8 period of time.

The results obtaining in vitro release studies were plotted in different models of the data treatment as follows:

- Cumulative percent drug released vs. time (zero-order rate kinetics)
- Log cumulative percent drug retained vs. time (First Order rate Kinetics)
- Cumulative percent drug released vs. square root of time (Higuchi's
- Classical Diffusion Equation)
- Log of cumulative % release Vs log time (Peppas Exponential Equations)

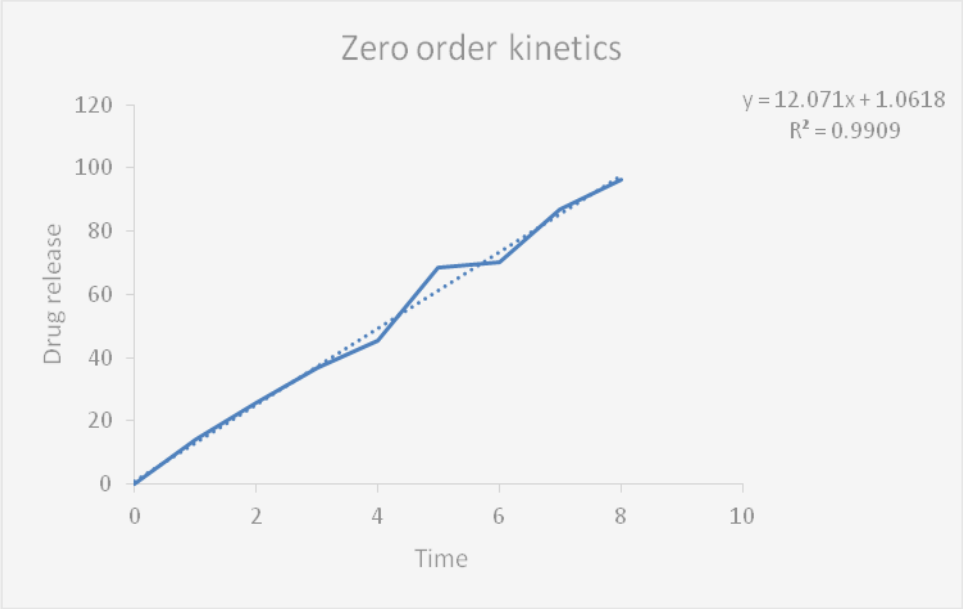

Fig.4. Zero-order kinetics

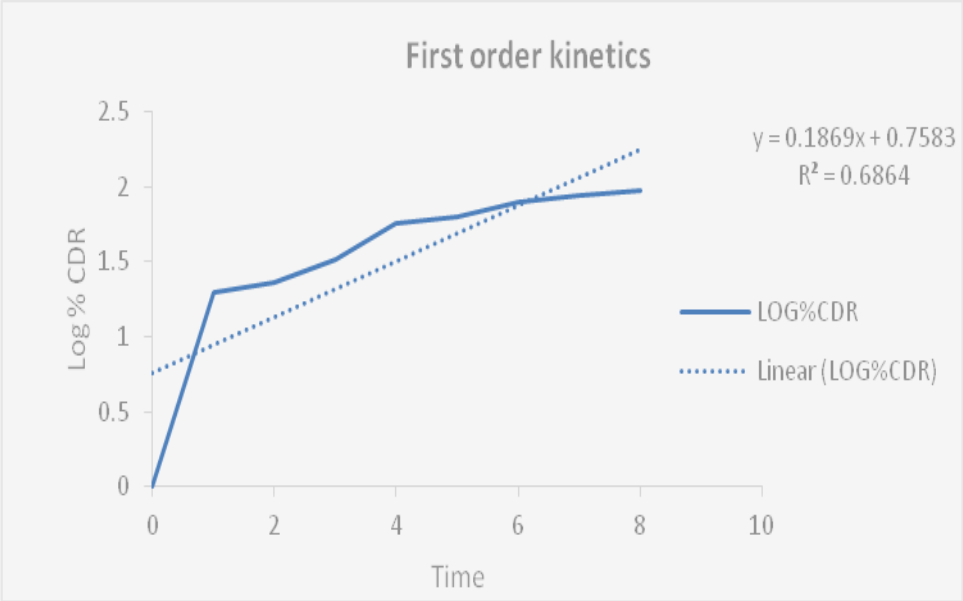

Fig.5. First order kinetics

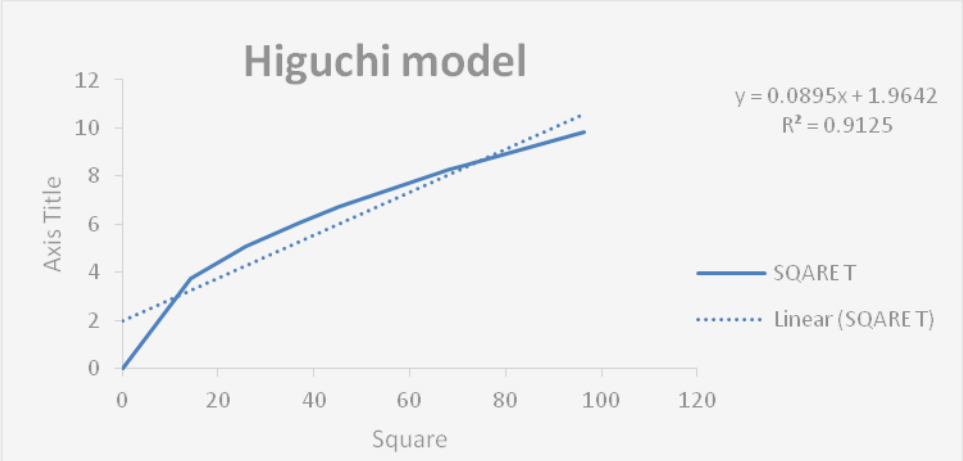

Fig.6. Higuchi model

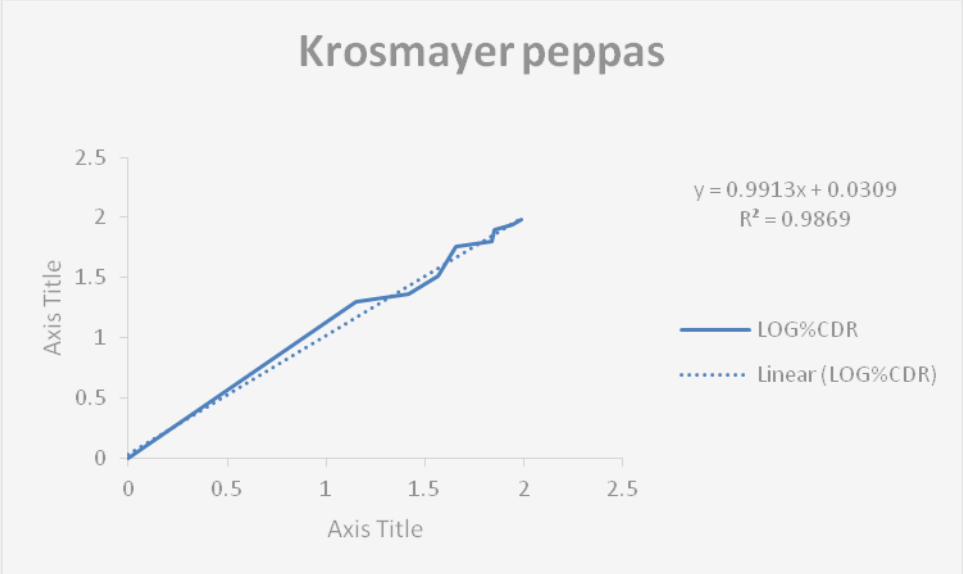

Fig.7. Korsmeyer Peppas

The values of in vitro release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi model, Peppas were respectively.

Regression values are higher with Zero-order release kinetics. Therefore, all the Rosuvastatin buccal patches have

Zero-order release kinetics. r^2 values are higher for Higuchi's model compared to all the formulations. Hence Rosuvastatin release from all the buccal films followed a diffusion rate-controlled mechanism.

Stability studies

Optimized formulations F2 were selected for accelerated stability studies as per ICH guidelines. The patches were observed for color, appearance, and flexibility for three months. The folding endurance, weight, drug content, % cumulative drug release of the formulation was found to be decreasing. This decrease may be attributed to the harsh environment (40^0C) maintained during the studies.

Table-: 4 Stability studies of optimized formulations

S.NO	Time in days	Physical changes	Mean % drug release		
			Rosuvastatin		
			25^0C/60%	30^0C/75%	40^0C/75%
1.	01	No Change	96.50	96.50	96.50
2.	30	No Change	95.15	95.09	95.99
3.	60	No Change	94.10	93.95	93.52
4.	90	No Change	93.99	93.52	93.15

V.SUMMARY AND CONCUSION

The present study was aimed to develop a new buccal patches system for the delivery of Rosuvastatin. An attempt was made to formulate Rosuvastatin buccal patches by the solvent casting technique. Literature review on polymers strongly indicated that polymers selected for the present study have bioadhesive and swelling forming properties. Different polymers were used like HPMCk 100 and PVP K40 were carried out. Different permeation enhancers were selected to study the effect of various permeation properties on selected Rosuvastatin buccal patches. Initially, preformulation studies were carried out to standardize a spectrophotometric method of estimation for Rosuvastatin and to investigate any possible drug-polymer interaction. Drug polymer interaction was studied by carrying out using FTIR studies. The FTIR studies have revealed that there was no drug-polymer interaction in the physical mixture Novel buccal patches of Rosuvastatin with unidirectional drug delivery were developed to overcome the first-pass metabolism of the Rosuvastatin. From this study, it is concluded that the buccal patches of Rosuvastatin can be formulated using PVP K 40 and HPMCk100 as the buccal patches polymers to obtain satisfactory unidirectional drug release with adequate bio adhesion. The in vitro studies have shown that this is a potential drug delivery system with a considerably good stability and release profile. All the analyzed formulations were equally good in their physicochemical characteristics. When compared to other formulations F2 formulation exhibited better in vitro drug release. The buccal film loaded with Rosuvastatin-calcium was used conveniently as an antilipemic agent.

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