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Research Article

Formulation and Evaluation of Buccal Patches of Rosuvastatin

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ABSTRACT

Mucoadhesive buccal patch of rosuvastatin were prepared by solvent casting technique using 1% hydroxypropylmethylcellulose, and variable amount of polymer sodium carboxymethylcellulose, polyvinyl alcohol (PVA) and polyvinyl pyrrolidine using propylene glycol as plasticizer as well as penetration enhancer. Prepared patch were evaluated for weight uniformity, thickness, surface pH, swelling index, *percent moisture absorption*, percent moisture lose, folding endurance, *in vitro* release, and drug content uniformity. The mean thickness of buccal polymeric patches increased with an increase amount of polymer percent. Percent swelling index determined at 5, 10, 30 and 60 minutes increased with time and with increase in hydrophilic polymer. HPMC-SCMC buccal patches show better swelling index because of presence of more hydroxyl group. The increase in the amount of polymer retarded the release of rosuvastatin.F1 (HPMC –SCMC) showed the maximum and faster release. From the study it was concluded that the films exhibited satisfactory swelling, and promising drug release. The formulation was found to be suitable candidate for the development of buccal patches for therapeutic use.

INTRODUCTION

The buccal region offers an attractive route for systemic drug delivery for extended periods of time. Bioadhesive formulations have a wide scope of applications, for both systemic and local effects of drugs [1]. Mucoadhesion has become of interest for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within gastrointestinal tract) or systemic delivery, by retaining a formulation in intimate contact with the absorption site (e.g. the buccal cavity) [2]. 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, therefore, avoiding the first pass hepatic metabolism and gastrointestinal drug degradation, which is associated with oral administration. The oral cavity is easily accessible for self-medication and, hence is well accepted by patients, and is safe, since device can be easily administered and even removed from the site of application, stopping the input of drug whenever desired[3].

The advantages reside on the reduction of drug dose because of its localization in the inflammatory process site. One particular problem to drug delivery system, aim to the treatment of the oral cavity disease, This problem may be resolved by using bioadhesive polymer i.e. - polymer that exhibits characteristic adhesive interaction with biological membrane[4]. Buccal films are also suitable for protecting wound surfaces, thus reducing pain and increasing treatment effectiveness. Rosuvastatin is an antilipidemic agent that competitively inhibits hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonic acid, the rate-limiting step in cholesterol biosynthesis. Rosuvastatin belongs to a class of medications called statin and is used to reduce plasma cholesterol levels and prevent cardiovascular disease.

Present study is undertaken to prepare Mucoadhesive Buccal film with aim to increasing the contact time achieving controlled release, reducing the frequency of administration and obtain greater therapeutic efficacy.

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Table 1: Composition of different buccal mucoadhesive formulation containing rosuvastatin

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rosuvastatin (mg)	20	20	20	20	20	20	20	20	20
HPMC	1%	1%	1%	1%	1%	1%	1%	1%	1%
SCMC	1%	1.5%	2%	-	-	-	-	-	-
PVPK-30	-	-	-	1%	1.5%	2%	-	-	-
PVA	-	-	-	-	-	-	1%	1.5%	2%
Methanol(ml)	3	3	3	3	3	3	3	3	3
Distilled Water(ml)	15	15	15	15	15	15	15	15	15
Propylene glycol(ml)	1	1	1	1	1	1	1	1	1

MATERIALS AND METHODS

Rosuvastatin was obtained as a gift sample from Ranbaxy Laboratory Ltd, Ponta Sahib (H.P). Hydroxypropylmethylcellulose, Polyvinyl alcohol (PVA), polyvinyl pyrrolidine k-30, and sodium carboxymethylcellulose (SCMC) were procured from Central Drug House pvt.Ltd. All other reagents used were of analytical grade. Concentration of rosuvastatin was measured with a UV-VIS spectrometer and polymers was verified using FTIR, and UV –VIS spectrophotometrically methods. The buccal films were prepared by solvent casting method.

Preparation of mucoadhesive buccal films [5]

Buccal films were prepared by solvent casting technique. HPMC, PVPK-30, SCMC, and PVA polymers were used in the preparation of buccal films. Propylene glycol, were used as a plasticizer as well as penetration enhancer. The polymers weighed accurately and dissolved in distilled water. The beaker containing polymer and distilled water was kept aside for 5 min for swelling of the polymer. Then propylene glycol was added to the polymer solution. Simultaneously drug accurately weighed and dissolved in 3ml of methanol in another beaker .The drug solution was added to the polymer solution and was mixed thoroughly with the help of magnetic stirrer .The whole solution was poured into the glass Petri dish place over a flat surface .Inverted funnel was placed over the dish to avoid sudden evaporation and allowed to dry overnight at room temperature to form a flexible film. The dried film were cut into size of 1x1 cm^2, packed in aluminium foil and stored in desiccators until further use.

Interaction studies

Interaction studies were conducted by comparing pure drug with polymers by IR Spectrophotometer. Infrared spectra were taken by using KBr pellet technique using a Perkin Elmer IR Spectrometer in the wavelength region of 4000to 400cm^{-1}.The procedure consisted of dispersing a sample (drug alone and mixture of drug and excipents) in KBr and compressing into discs by applying a pressure of 5 tons for 5 minutes in hydraulic press. The pellet was placed in a light path and the spectrum was obtained.

Evaluation of Mucoadhesive Buccal patch of Rosuvastatin

1. Film weight and thickness

For evaluation of film weight three films of every formulation were taken and weighed individually on a digital balance. The average weights were calculated. Similarly, three buccal films of each formulation were taken and the film thickness was measured using micrometer screw gauge at three different places and the mean value was calculated[6, 7].

2. Folding endurance

Folding endurance of the film was determined by repeatedly folding a small strip of film at the same place till it breaks. The number of times films could be folded at the same place, without breaking gives the value of folding endurance[8].

3. Surface pH of the patches

Formulation was allowed in contact with 1 ml of distilled water. The surface pH was noted by bringing a combined glass electrode near the surface of the patches and allowing equilibrate for 1 min[9].

4. Swelling studies of the patches

The polymeric patches cut into 1x1cm^2 were weigh accurately and kept immersed in 20ml of water .The patches were taken out carefully at 5, 10 up to 60 minutes intervals, blotted with filter paper to remove the water present on their surface and weigh accurately, the percent

swelling is calculated .The weight of the swollen film was noted (W2).The swelling index was calculated by the formula[10].

$$\text{Swelling index} = (W2-W1)/W1\times100$$

Where W1=Dry weight of the film
W2 =Wet weight of the film

5. Content uniformity

To determine the drug content uniformity, three film units of each formulation were taken in separate 100ml volumetric flasks, 100 ml methanol was added and continuously stirred. The solutions were filtered, diluted suitably and analyzed at 245nm in a UV spectrophotometer. The average of drug contents of three films was taken as final reading[11].

6. Percentage moisture absorption (PMA)

Films were preweighed accurately and kept in desiccators containing 100 ml of saturated solution of potassium chloride .After 72hrs (3 days), the films were taken out, weighed and percentage moisture absorption was calculated[12].

$$\% \text{ moisture absorption} = \frac{(\text{Final weight} - \text{Initial weight})}{\text{Initial weight}} \times 100$$

7. Percentage moisture loss

Percentage moisture loss was also carried to check the integrity of films at dry condition. Patches were pre-weighed accurately and kept in desiccators' containing fused anhydrous calcium chloride. After 72 hours the films were removed, weighed. And percentage moisture loss was calculated[12].

$$\% \text{ moisture Loss} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \times 100$$

8. *In-vitro* drug release studies of formulations

In- vitro drug release study was performed by attaching egg membrane to one end of the open cylinder which acted as donor compartment .Prepared buccal patch containing drug was placed inside the donor compartment .Receptor compartment consist phosphate buffer pH 6.8 which continuously stirred using a magnetic stirrer and the temperature was maintain at 37C°.The samples were withdrawn at different time intervals and analyzed for drug content by UV spectroscopy .The receptor phase refilled with an equal volume of phosphate buffer at each sample withdraws[13].

Release kinetics

The dissolution data was fitted to a Zero order, First order ,Higuchi and Korsmeyer –peppas to ascertain the kinetics modeling of the drug release .The method was adopted for deciding the most appropriate model .Data of in vitro release was fit into different equations to explain the release kinetics of rosuvastatin release from buccal patches. The kinetic equations used were zero order and first order equations.

Zero order release kinetics

It defines a linear relationship between the fractions of drug released verses time:

$$\mathbf{Q=kt}$$

Where, Q is the fraction of drug released at time t and k is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First order release kinetics:

Wagner assuming that the exposed surface area of a formulation decreased exponentially with time during dissolution process suggested that drug release from most slow release formulation could be described adequately by apparent first order kinetics .The equation used to describe first order release kinetic is

$$\mathbf{In\ (1-Q) = -kt}$$

Where,Q is the fraction of drug released at time t and k is the first order release rate constant .Thus ,a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi (Diffusion) equation:

It defines a linear dependence of the active fraction released per unit of surface on the square root of time.

$$\mathbf{Q = kt1/2}$$

Where, k is the release rate constant .A plot of the fraction of drug released against square root of time will be linear if release obeys higuchi equations. This equation describes drug release as a diffusion process based on the flick's law, square root time dependent.

Korsmeyer –peppas kinetics

A plot of the fraction of the logarithm of % drug released against logarithm of time will be linear if the release obeys Korsmeyer –peppas equation.

$$\text{Log } Q = \log k + n \log t$$

Where, k is the release rate constant.

RESULTS AND DISCUSSION

Buccal films of rosuvastatin were prepared by solvent casting technique with the use of mucoadhesive polymers such as HPMC 1% and variable amount of different polymer composite, SCMC, PVPK-30, PVA. The buccal patches prepared using propylene glycol used as a plasticizer as well as penetration enhancer. The prepared films were evaluated for different physicochemical tests such as weight variation, thickness, content uniformity, swelling index, surface pH, % Moisture absorption, % Moisture loss, and *in vitro* drug release studies. Here figure1 shows the calibration curve of rosuvastatin.

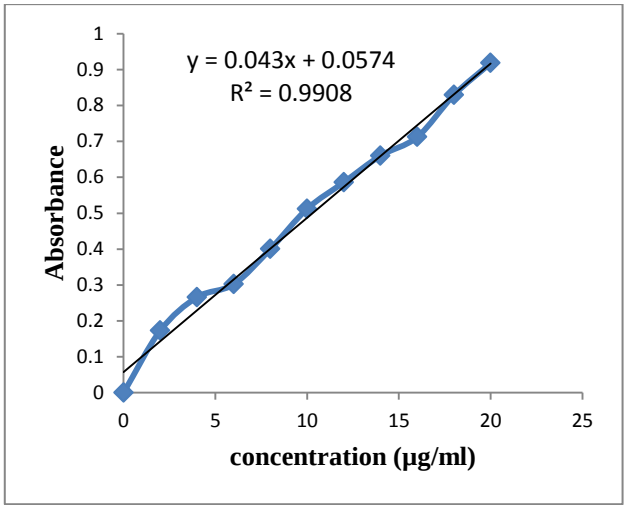

Figure 1: Calibration curve rosuvastatin

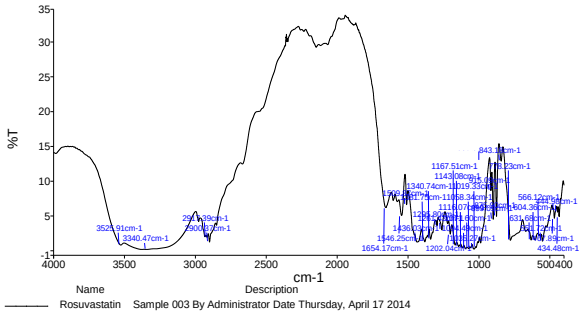

Figure 2: FTIR Spectra of Rosuvastatin

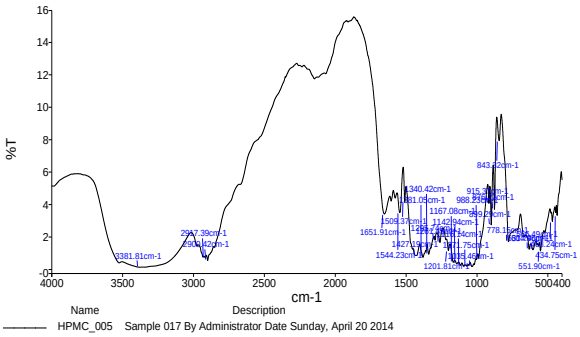

Figure 3: FTIR Spectra of Rosuvastatin+HPMC

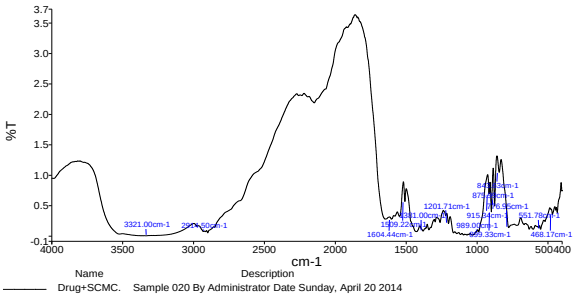

Figure 4: FTIR Spectra of Rosuvastatin+SCMC

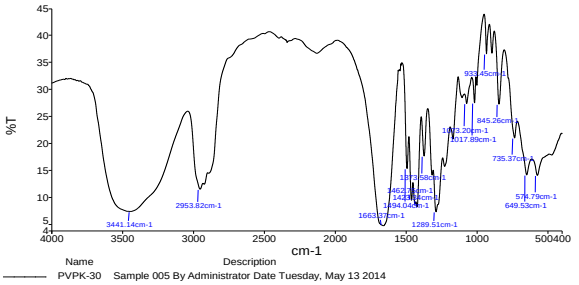

Figure 5: FTIR Spectra of Rosuvastatin+PVPK-30

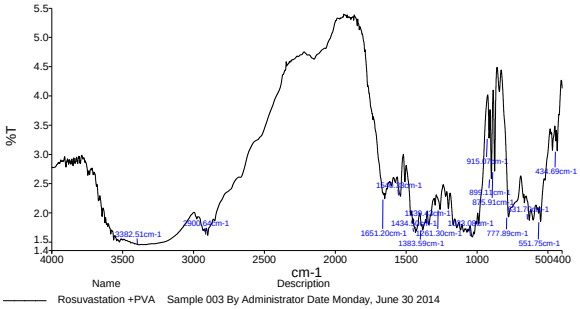

Figure 6: FTIR Spectra of Rosuvastatin+PVA

The graph obtained of drug sample was compared with the graph of rosuvastatin given in IP and analytical profile of drug substances. The two graphs match with each other it shows that the drug sample use is pure and stable.

Table 2: Thickness, weight uniformity and folding endurance of buccal patches of rosuvastatin

S.NO.	Formulation Code	Thickness (mm) ±S.D(n=3)	Weight Uniformity (mg) ±S.D (n=3)	Folding Endurance ±SD.(n=3)
1	F1	0.29±0.002	110.33±0.58	178.5±4.62
2	F2	0.31±0.008	130.33±0.57	187.5±8.12
3	F3	0.33±0.006	141.00±0.58	165±12.22
4	F4	0.28±0.006	150.33±0.58	163±2.0
5	F5	0.30±0.004	162.33±1.00	162.5±5.87
6	F6	0.35±0.002	170.00±1.00	167.0±5.87
7	F7	0.36±0.005	180.33±0.57	172±2.0
8	F8	0.41±0.004	190.33±1.52	178±1.53
9	F9	0.42±0.002	210.33±0.58	185±3.51

Table 3: Surface pH, Percentage moisture absorption, Percentage moisture loss

S.NO	Formulation Code	Surface pH ± S.D(n=3)	%Moisture absorption ±SD(n=3)	%Moisture loss ±SD(n=3)
1	F1	6.15±0.10	2.84±0.015	1.42±0.01
2	F2	6.42±0.03	3.88±0.015	1.24±0.01
3	F3	6.59±0.02	2.93±0.092	0.96±0.41
4	F4	6.50±0.02	2.95±0.070	1.06±0.02
5	F5	6.22±0.10	4.07±0.075	1.06±0.02
6	F6	6.31±0.01	5.49±0.820	1.16±0.02
7	F7	6.67±0.02	5.74±0.810	3.82±0.17
8	F8	6.72±0.05	7.17±0.07	4.57±0.04
9	F9	6.45±0.02	7.31±0.14	6.25±0.09

All the films showed uniform thickness throughout. The mean thickness of buccal polymeric patches increased with an increase in the amount of polymer percent. The film thickness was observed to be in the range 0.28±0.006 to 0.42±0.002 mm. The weights of different formulation were found to be in the range of 110.33±0.58 to 210.33±0.58 mg. The acidic or alkaline pH may cause irritation to buccal mucosa and may affect the drug release and degree of hydration of polymers. Therefore the surface pH of buccal patch was determined to optimize both drug release and mucoadhesion. The surface pH of all formulations was within range of 6.15±0.10 to 6.72±0.05 and hence no mucosal irritation was expected and ultimately achieves patient compliance. Folding endurance was measured manually by folding the film repeatedly at a point till they broke. The folding endurance was found to be in the range of 162.5±5.87to 185±3.51. The results of content uniformity indicated that the drug was uniformly dispersed; the content was in range of 17.7±0.01 to 19.92±0.17 mg/cm2. The range of %Moisture absorption of buccal polymeric patch lies within the range2.84±0.015 to7.31±0.14 and the range of %Moisture loss of buccal polymeric patch lies within the range 0.096±0.41 to 6.25±0.09. Percent swelling index determined at 5, 10, 30 and 60 minutes increased with the time and with an increase in hydrophilic polymer. Sodium carboxy methyl cellulose showed high % swelling because of the presence of more hydroxyl group.

Table 4: Drug content uniformity of rosuvastatin buccal patch

S.NO	Formulation Code	Drug content uniformity ±S.D(n=3)
1	F1	17.7±0.01
2	F2	17.8±0.01
3	F3	18.3±0.01
4	F4	18.78±0.08
5	F5	18.90±0.08
6	F6	18.2±0.01
7	F7	19.92±0.17
8	F8	19.66±0.17
9	F9	19.58±0.17

Table 5: Percentage swelling index in time (min)

Time(minutes)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	4.12	3.14	3.87	3.80	2.81	3.43	4.61	2.14	5.03
10	6.12	6.28	5.91	5.19	9.34	8.13	9.11	9.81	10.31
15	9.32	11.04	9.08	12.31	11.18	14.08	16.81	13.19	17.81
20	13.82	16.34	15.31	13.00	15.61	19.11	21.38	20.08	22.31
30	20.14	26.28	23.13	18.41	23.10	27.81	29.34	25.03	30.81
60	29.04	31.24	35.49	24.77	30.01	31.91	39.12	40.83	42.01

In-vitro release studies

In vitro release studies of various formulations were performed using pH 6.8 phosphate buffer as dissolution medium. The drug concentration was determined spectrophotometrically at 245nm. Significant difference was observed in the release pattern of rosuvastatin patch containing HPMC, PVA, PVPK-30 and SCMC. In vitro release characteristics of rosuvastatin buccal patches showed decrease in percent release with an increase in the amount of polymer , *In –vitro* releases for all formulation shown in phosphate buffer 6.8 and all formulation data lies within the range from 70.12-94.02 up to 8 hrs .The first three ;F1, F2 and F3 formulation of Drug :HPMC : PVA combination shown drug release 80.1,78.3 and 70.12 respectively and for formulation F4,F5 andF6 of Drug :HPMC:PVPK-30 combination shown drug release 90.80 ,87.4 and 85.01 respectively and for formulation F7,F8 andF9 of Drug:HPMC:SCMC 94.02,89.3 and 85.3respectively. F3 (HPMC: PVA) showed the minimum and slower release and F7 (HPMC: PVA) showed maximum and faster release.

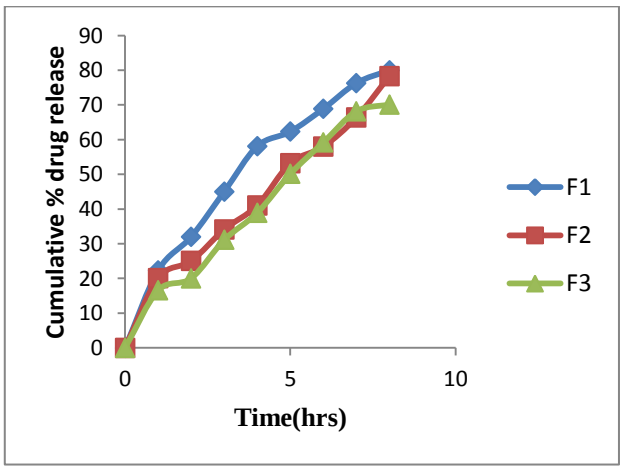

Figure 7: *In -vitro* drug release kinetic plot from F1, F2, and F3 formulations of rosuvastatin

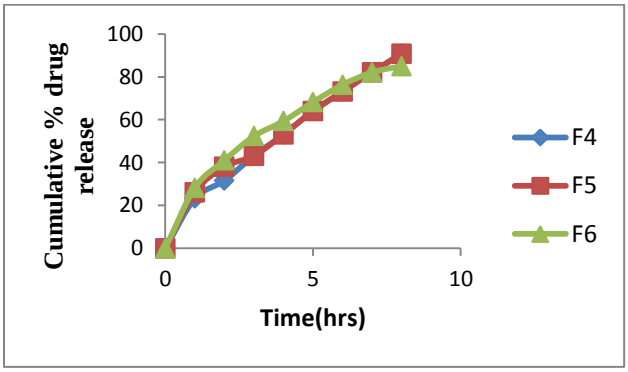

Figure 8: *In- vitro* release kinetic plot from F4, F5, and F6 formulations of rosuvastatin

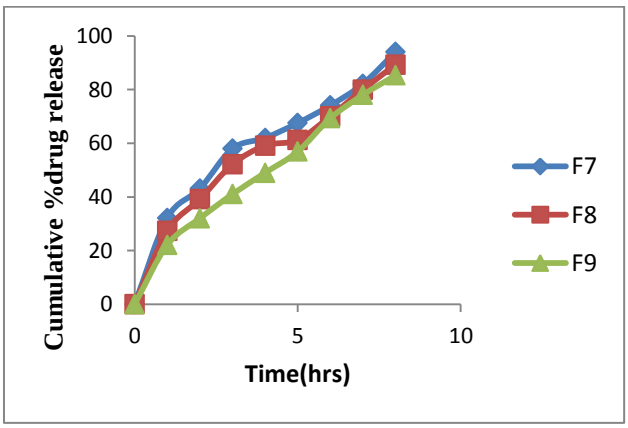

Figure 9: *In- vitro* release kinetic plot from F7, F8, and F9 formulations of rosuvastatin

CONCLUSION

The results of the study show that therapeutic levels of rosuvastatin can be delivered buccally. The present study concludes that these erodible mucoadhesive buccal films containing rosuvastatin can be very promising for effective doses to systemic circulation. These may also provide an added advantage of circumventing the hepatic first pass metabolism. From the present study carried out on rosuvastatin buccal patches prepared from 1% HPMC and variable amount of different polymer composite ,PVP K-30,PVA,SCMC .The buccal patches prepared using propylene glycol were found to have good

good physical characteristics .The mean thickness of buccal polymeric patches increased with an increase in the amount of polymer percent. Percent swelling index determined at 5, 10, 30 and 60 minutes increased with time and with an increase in hydrophilic polymer. Thus one may conclude that these polymer systems of HPMC along with PVP K-30, PVA, and SCMC have potential for consideration for drug delivery as buccal dosage forms.

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