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Development and Characterization of Mucoadhesive Product of Atorvastatin

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ABSTRACT

Atorvastatin Calcium (ATC) used for lowering the cholesterol levels in body. It is competitive inhibitor of hydroxyl methylglutaryl-coenzyme A (HMG-CoA) reductase, followed mevalonate pathway, which have low bioavailability and poor solubility. Present work focus on development of mucoadhesive buccal patches of atorvastatin calcium, for improve the delayed transit, continuous longer period release Mucoadhesive formulations of atorvastatin were made by solvent casting method. The patch formulations were incorporated with mucoadhesive polymers like Hydroxypropyl methyl Cellulose (HPMC K-15M), Poly vinyl alcohol (PVA), Poly Vinyl Pyrrolidone (PVP K-30) and Ethyl Cellulose (EC). Microspheres were characterized in terms of physicochemical parameters, micromeritic properties, FT-IR, and mucoadhesive wash-off test and ex-vivo permeation study. All prepared formulations indicated good physical stability. These novel unidirectional buccal patches can be considered as alternative to oral route of administration of atorvastatin. This route may also provide additional advantages of bypassing the first pass metabolism and ease of administration for heart patients.

KEYWORDS: Atorvastatin, Heart patients, Buccal Patches, in-vitro Permeation Study

INTRODUCTION

Atorvastatin Calcium [(3R,5R)-7-[2- (4-fluorophenyl)-3-phenyl4-(phenylcarbamoyl)-5-propan-2-ylpyrrop1yl]-3,5-dihydroxyheptanoic acid [ATC] is a member of the drug used for lowering the cholesterol levels in body. The primary uses of atorvastatin calcium are for the treatment of disease like dyslipidemia and the prevention of cardiovascular disease. [1-3] It is competitive inhibitor of hydroxyl methylglutaryl-coenzyme A (HMG-CoA) reductase, followed mevalonate pathway. The rate-determining enzyme in cholesterol biosynthesis via the mevalonate pathway. [4,5] In mevalonate pathway HMG-CoA convert to mevalonate in presence of catalyses HMG-CoA reductase. ATC is primarily act on liver cells. In which decrease the hepatic and plasma cholesterol levels. [6,7] ATC showed low bioavailability and poor solubility. The rate of absorption of ATC was maximum found in the upper GI tract. [8,9] Therefore, mucoadhesive drug bioavailability. Mucoadhesive drug system provides the targeted controlled and sustained release of ATC for longer period of time. [10] It is based on delayed transit and continuous release system, so it lives in prolong residence in GIT especially in colon, along with their release. [11]

The buccal mucosa, along with other mucosal tissues, has been investigated as a potential site for controlled delivery of macromolecular therapeutic agents, such as peptides, proteins and polysaccharides because of its accessibility and low enzymatic activity compared to the gastro-intestinal tract [12, 13]. The potential of the buccal mucosa as an alternative site for the delivery of drugs into the systemic circulation has recently received much attention. There are various reasons, why the buccal mucosa might be an attractive site for the delivery of therapeutic agents into the systemic circulation. [14 – 16].Due to the direct drainage of blood from the buccal epithelium into the internal jugular vein, the first pass metabolism in the liver and intestine may be avoided. This first-pass effect is a major reason for the poor bioavailability of some compounds, when administered orally. Additionally, the mucosal lining the oral cavity is easily accessible, which ensures that a dosage form can be applied to the required site and removed easily in case of emergency. The film is an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market, is easy to handle and administration, maintains a simple and convenient packaging, alleviates unpleasant taste, and is easy to manufacture. The film is placed on the top or the floor of the tongue [17, 18]. It is retained at the site of application and rapidly releases the drug for local and systemic absorption [19]. Oral fast dissolving film is one such novel approach to increase consumer acceptance by virtue rapid dissolution, self administration without using water or chewing.

Thus, there is a growing interest in developing alternative dosage forms, i.e. orally fast disintegrating strip, which allow a rapidly dissolving drug to absorb directly into the systemic circulation through the oral mucosa [20]. These kinds of dosage forms are also convenient for children, elderly patients with swallowing difficulties, and in the absence of potable liquids. However, in addition to formulation considerations, the properties of the active compound have to be appropriate in order to achieve drug delivery into systemic circulation after intraoral administration. In this article attempt has been made to fabricate transdermal patches of Atorvastatin by using polymer like HPMC and ethyl cellulose to provide sustained or controlled release of incorporated drug atorvastatin.

2. MATERIALS AND METHODS

Materials: The drug atorvastatin procured from Aarti Drug Limited., Mumbai. The materials used in this study were following: Hydroxy Propyl Methyl Cellulose, Chitosan, Ethyl Cellulose, Poly polyvinyl alcohol, Poly Vinyl Pyrrolidone and ethylene glycol-400 as plasticizer. All other laboratory materials were of analytical grade.

FTIR Spectroscopy: Fourier transform infrared spectroscopy (FT-IR, Shimadzu, Model-RT-IR-8300) is a technique mostly used to identify organic, polymeric, and some inorganic materials as well as for functional group determination. Fourier Transform Infrared Analysis (FTIR) measurements of pure drug, polymer and drug loaded polymer formulations were obtained on FTIR. The pellets were prepared on KBr-press under hydraulic pressure of 150 kg/cm^2; the spectra were scanned over the wave number range of 3600 to 400 cm^{-1} at the ambient temperature. [21]

UV Spectroscopy: 20µg/ml concentration of solution Atorvastatin was prepared in dilution. The resulting solution was scanned in UV-Visible spectro-photometer from 200-400 to determine the λ_{max}.[22]

Drug Excipients Compatibility studies: Excipients are the substances which are included along with the API in the pharmaceutical dosage forms. As most of the excipients having no direct pharmacological action but these are important for administration and modulating the accurate release of active substance and maintaining API against degradation and increasing the size of the dosage form and masking the bitter taste an increases the patient compliance and the studies of drug – excipient compatibility interactions between potential formulation excipient the API in the development stage of all dosage forms FT-IR spectroscopy study was carried to assess the compatibility between atorvastatin, HPMC and Ethyl cellulose. The pure drug and drug with excipients were separately scanned. The pellets were prepared on potassium bromide press. Both the spectra were compared for confirmation of peaks. [23]

Formulation Of Transdermal Patches: Mucoadhesive formulations of atorvastatin were made by solvent casting method. The patch formulations were incorporated with mucoadhesive polymers like Hydroxypropyl methyl Cellulose (HPMC K-15M), Poly vinyl alcohol (PVA), Poly Vinyl Pyrrolidone (PVP K-30) and Ethyl Cellulose (EC). To prepare various proportions of polymers, different stock solutions were used. A 2% w/v stock solution of HPMC K-15M was prepared in distilled water and solution of PVA was also prepared in 2% w/v concentration. Another stock solution of PVP K-30 and EC in 1% w/v concentration was also prepared in water and ethanol respectively. The proportion of polymer mixture used in formulations was given in Table 1. [24]

The volume of liquid used in mould to make patches was kept constant as Polyethylene glycol (PEG- 400) 2 mL was mixed in above polymer mixture. To the above polymer mixture, alcoholic solution of atorvastatin calculated quantity (188mg/5 mL) which makes the concentration of 20 mg per unit of buccal patch (3 cm diameter) was included. The solution of polymer and drug was homogenized and poured into Teflon coated Petri dish (9.2 cm diameter) by carefully placing on a horizontal surface. The Petri dish mould was covered with a glass funnel to ensure uniform evaporation. The Petri dish content were initially dried at room temperature for 2 h and additionally dehydrated in a hot air drier at 50 ºC for 48 h. The circular disc of dried patches were removed from mould and examined visually for deformation if any. Then buccal patch units (3 cm diameter) were cut from the circular disc, so that each unit of patch may contain 20 mg of atorvastatin. All the prepared patches were converted into unidirectional release formulation by pasting BOPP film backing layer (Pidilite®) on one side with acrylic adhesive then all patched were preserved in an aluminum foil and stored in a desiccator. [25]

Table 1: Compositions Of Transdermal Patches

Formula code	Drug (mg)	HPMC-K15M (2%, w/V) (ml)	EC (1%, w/V) (ml)	PVA (2%, w/V) (ml)	Plasticizer PEG- 400 (mL)	PVK-30 (1%,w/V) (ml)
FAP1	20	10	10	10	2	-
FAP 2	20	12	6.0	12	2	-
FAP 3	20	13.3	3.3	13.3	2	-
FAP 4	20	12	12.0	6.0	2	-
FAP 5	20	15	7.5	7.5	2	-
FAP 6	20	17.2	4.3	8.6	2	-
FAP 7	20	13.3	13.3	3.3	2	-
FAP 8	20	17.2	8.6	4.3	2	-
FAP 9	20	20	5.0	5.0	2	-
FAP 10	20	10	-	10	2	10
FAP 11	20	12	-	12	2	12
FAP 12	20	13.3	-	13.3	2	13.3
FAP 13	20	12	-	6.0	2	6.0
FAP 14	20	15	-	7.5	2	7.5
FAP 15	20	17.2	-	8.6	2	8.6
FAP16	20	13.3	-	3.3	2	3.3
FAP17	20	17.2	-	4.3	2	4.3
FAP18	20	20	-	5.0	2	5.0

*Total volume of 30ml was maintained excluding plasticizer.

Evaluation Of Transdermal Patches

Physical Appearance: All the prepared patches were visually inspected for color, clarity, flexibility, and smoothness.

Film Thickness: The thickness was measured at six different places using an Electronic Digital Micrometer (AEROSPACE-CHINA) and the mean Value was calculated.

Average Weight and Weight Variation: As weight variation between the formulated patches can lead to difference in drug content and in-vitro behaviour, a study was carried out by weighing 6 patches in an electronic balance. [26]

Determination of Tensile Strength: The instrument, which was designed in our laboratory, was used for the measurement of tensile strength. The weight required to break the film was noted as the break force. The tensile strength was calculated using Allen's formula.

Tensile Strength = Break Force x (1 + ΔL) / a x b L

Folding Endurance: Folding endurance of the film is determined by repeatedly folding one film at the same place till it broke, which was considered satisfactory to reveal good films properties. The number of times of films could be folded at the same place without breaking gave the value of the folding endurance. This test was done on randomly selected three films from each formulation. [27]

Determination Of Drug Content: A formulated patch having 15.21 cm^2 area was cut into small pieces and transferred into a graduated glass stoppered flask, which contained 100ml of mixture of chloroform and methanol in the ratio of 1:1, maintained at 45-50˚C. The procedure was carried out in duplicate to determine the drug content. The following procedure was carried out induplicate to determine the drug content.

Swelling study: The study of swelling was done by placing patches on the wet surface of agar prepared by using 2 % (w/v) agar dissolved in hot simulated saliva (pH 6.2). Initially the weight of patch without BOPP layer was measured in a digital balance (W_0). The swelling of patches on the agar surface for 2 h was permitted at 37 ºC± 0.2 ºC of incubation. The increase in weight of the swelled patches was noted (W_t) at specified time intervals till to reach saturation. [28] The percentage of swelling (%S) occurs was determined from the following equation:

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$$\%S = W_t - W_o / W_o \times 100$$

Here,

W_t is the measured weight of patch at time t,

W_o is the initial weight of non-swollen patch measured at t=0

Ex Vivo Mucoadhesion Time: The ex vivo study of Mucoadhesion time of patches gives information related to the duration of residence of patches at the site of Mucoadhesion. This study was done in a USP disintegration apparatus which was modified to hold a glass slide with mucus membrane. The experiment was repeated thrice for minimizing deviation.

Ex vivo mucoadhesive strength: The study of mucoadhesive strength was done by measuring the detachment force required to separate buccal patches from the mucus membrane. [29] The force of Mucoadhesion was also calculated from the following equation:

Mucoadhesive Strength (g) $= \frac{\text{Mucoadhesi ve strength(g)}}{1000} \times \text{accelerati on due to gravity}$

Here, acceleration due to gravity is 9.8 ms^{-2}.

In-vitro Drug Release Study: The study of in vitro release of atorvastatin was executed in a modified Franz diffusion cell with inner diameter of 3cm and receptor compartment height of 14 cm was used for the study.

Release kinetic study: The drug release and mechanism it follows to release can be determined by matching the data with various release models like Higuchi, Korsmeyer-Peppas, zero order and first order plots. [30, 31]

Accelerated Stability Studies: The optimized formulations were uniformly packed in aluminum films and arranged in Petri plates. Then the samples were stored in stability chamber for accelerated stability testing as per ICH guidelines. The samples were subjected to temperature of 40 ± 2ºC and humidity 75 ± 5% RH for the duration of 6 months. [32]

RESULTS AND DISCUSSION

FTIR Spectra of Drug: FT-IR spectroscopy was used to determine the functional group present in the pure drug sample. Spectra of Atorvastatin had shown characteristic peak at 2933.74 cm^{-1} (C-H – stretching), 1314.81 cm^{-1} (C-N – stretching), 3061.91 cm^{-1} (C-HO -stretching alcoholic group), 1568.04 cm^{-1} (C=O – stretching amidic group), 3382.29 cm^{-1} (N-H - stretching), 1651.82 cm^{-1} (C=C - bending), 752.30 cm^{-1}, 691.50 cm^{-1} (C-F- stretching), 1157.10 cm^{-1} (O-H- bending).

UV Spectroscopy: The 20µg/ml Atorvastatin calcium was scanned in UV-Visible spectrophotometer from 200-400nm to determine the λ_{max}. The λ_{max} was found to be at 242nm so, the calibration of Atorvastatin calcium was developed at this wavelength.

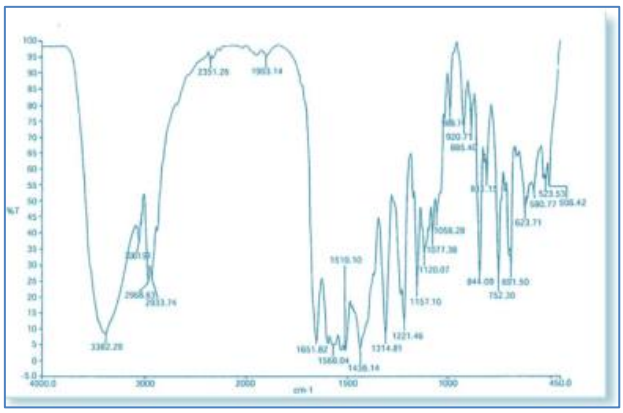

Figure 1: FTIR Spectra of Pure Drug Atorvastatin

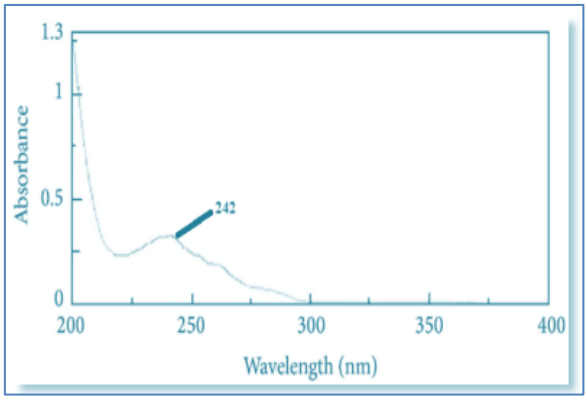

Figure 2: UV Spectra of Atorvastatin

Drug Excipient Compatibility Studies: As the interaction studies were performed to find any kind of interaction between drug and excipients used in formulation. FT-IR spectroscopy was used to determine the functional group present in the pure drug ample.

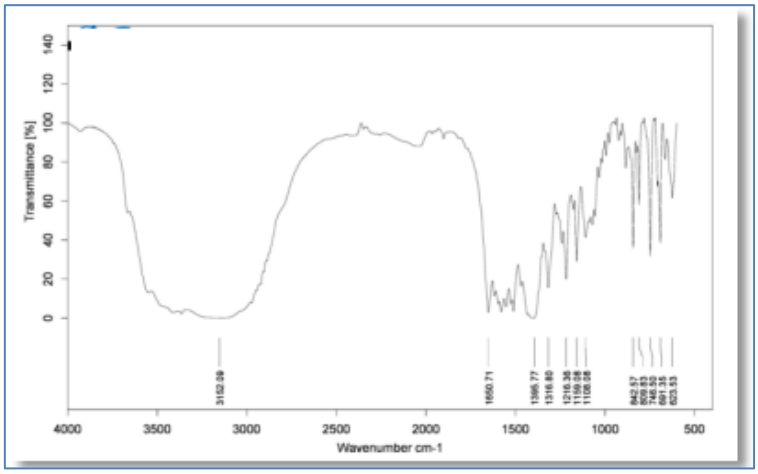

Figure 3: FTIR Spectra of atorvastatin + HPMC

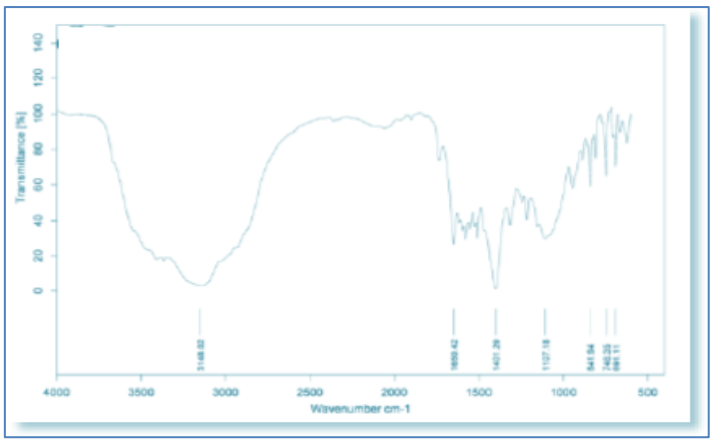

Figure 4: FTIR Spectra of atorvastatin + EC

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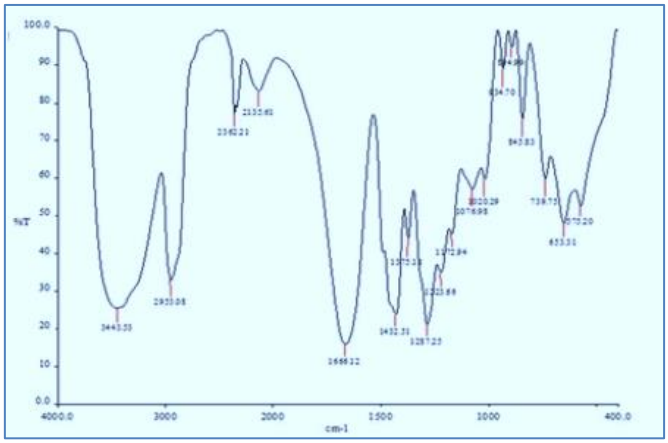

Figure 5: FTIR Spectra of atorvastatin + PVA

Formulation and Development: Transdermal drug delivery system of Atorvastatin was developed using polymers like HPMC, EC, employing PEG-400 as plasticizer. Formulated 18 patches were subjected to physico- chemical evaluation such as physical appearance, weight variation, thickness, % moisture content, % moisture uptake, tensile strength, hardness and drug content. The in vitro drug release studies across cellulose membrane were conducted and the best formulations where subjected to stability studies. 18 patches formulation of atorvastatin loaded with different ratios of HPMC, PVA, PVP, EC were prepared by solvent casting methods.

Evaluation Parameters: The determination of the average weight of patch, having 14.87 cm^2 surface area showed a significant change between the patches prepared with different polymer ratios. The average weight of the patches FAP- FAP18 were given in the table: 4.4. There was no significant change in the thickness of the patches (FAP1-FAP18), which was determined by aerospace digital electronic micrometer. This indicates that the patches were uniform and reproducible. The thickness in all prepared formulations varied between the range 0.231±0.022 to 0.401±0.019. The tensile strength in all prepared formulations varied between the range 1.699 to 1.775. The Drug Content in all prepared formulations varied between the range 0.5601 to 0.5698. The folding endurance was found to be 3.99±0.21 to 5.75±0.23 of formulation FAP1-FAP18, KTP10 and KTP15 respectively. Tensile strength was found to be higher for the patches KTP1- KTP7 when compared to other patches and hardness is found to be low for the patches KTP8-KTP18 when compared to other patches. All the patches showed uniform drug content, which was determined using SHIMADZU UV- 1700 spectrophotometer.

Table 2: Average Weight, Weight Variation and Thickness

Formula code	Physical Appearance	Weight Variation (mg)	Thickness (mm)
FAP1	Transparent, Flexible, Smooth	0.332±0.005	0.231±0.022
FAP 2	Transparent, Flexible, Smooth	0.375±0.005	0.243±0.021
FAP 3	Transparent, Flexible, Smooth	0.275±0.006	0.245±0.026
FAP 4	Transparent, Flexible, Smooth	0.317±0.004	0.312±0.019
FAP 5	Transparent, Flexible, Smooth	0.329±0.005	0.245±0.024
FAP 6	Transparent, Flexible, Smooth	0.354±0.004	0.243±0.024
FAP 7	Transparent, Flexible, Smooth	0.327±0.005	0.302±0.023
FAP 8	Transparent, Flexible, Smooth	0.384±0.005	0.401±0.019
FAP 9	Transparent, Flexible, Smooth	0.337±0.004	0.312±0.018
FAP 10	Transparent, Flexible, Smooth	0.331±0.006	0.276±0.019
FAP 11	Transparent, Flexible, Smooth	0.299±0.006	0.287±0.019
FAP 12	Transparent, Flexible, Smooth	0.316±0.005	0.311±0.021
FAP 13	Transparent, Flexible, Smooth	0.376±0.004	0.286±0.016
FAP 14	Transparent, Flexible, Smooth	0.331±0.003	0.287±0.012
FAP 15	Transparent, Flexible, Smooth	0.299±0.006	0.319±0.021
FAP16	Transparent, Flexible, Smooth	0.386±0.006	0.375±0.065
FAP17	Transparent, Flexible, Smooth	0.299±0.007	0.353±0.011
FAP18	Transparent, Flexible, Smooth	0.342±0.006	0.353±0.056

Table 3: Folding Endurance, Tensile Strength and Drug Content

Formula code	Folding Endurance	Tensile Strength(kg/cm^2)	Drug Content(mg/cm^2)
FAP1	4.24±0.12	1.756	0.5634
FAP 2	4.28±0.22	1.746	0.5643
FAP 3	4.55±0.32	1.746	0.5621
FAP 4	4.71±0.50	1.747	0.5628
FAP 5	4.65±0.34	1.748	0.5629
FAP 6	4.67±0.51	1.739	0.5623
FAP 7	4.65±0.52	1.775	0.5645
FAP 8	3.99±0.21	1.756	0.5631
FAP 9	4.08±0.78	1.734	0.5599
FAP 10	4.21±0.12	1.723	0.5601
FAP 11	4.78±0.52	1.715	0.5621
FAP 12	4.61±0.65	1.709	0.5642
FAP 13	4.98±0.52	1.699	0.5639
FAP 14	4.53±0.62	1.721	0.5635
FAP 15	4.98±0.59	1.654	0.5631
FAP16	4.11±0.56	1.5678	0.5681
FAP17	5.75±0.23	1.623	0.5689
FAP18	4.67±0.56	1.716	0.5698

Swelling Study: A controlled swelling was observed among the tested atorvastatin buccal patches and the values of swelling index were found to be diverse between the formulations. These changes might be the result of variations in the combination of the hydrophobic and hydrophilic polymers kept in the formulations. The swelling measurements of atorvastatin patches at various time intervals were exemplified in **Table 4.** The percentage of swelling was found to be much more up to 63 ± 4 % for patches FA16 at 120 min of study. The rate of swelling was observed in the following ascending order, FAP10< FAP8< FA1< FAB2< FAB14< FAB16. The swelling behavior is directly related to the relative moisture uptake nature of polymers and thereby provides information related to formulations and their integrity after absorption of moisture.

Table 4: Swelling behavior of HPMC and PVA buccal patches of Atorvastatin

Time (min)	Percentage of Swelling (%) *					
	FAP1	FAP2	FAP8	FAP10	FAP14	FAP16
0	0	0	0	0	0	0
5	9±1.54	7±3.22	5±2.45	12±2.67	14±4.54	19±1.53
10	13±3.45	11±4.45	8±3.33	18±4.48	19±2.24	26±1.56
15	17±5.32	17±1.54	14±2.46	22±2.11	26±1.54	34±3.42
30	22±3.23	20±2.56	18±1.44	28±4.25	32±1.23	40±2.45
45	28±1.23	24±2.53	24±2.12	32±4.45	38±2.51	47±3.33
60	31±2.67	29±3.34	27±3.21	38±1.75	43±2.55	52±1.96
90	36±1.67	33±2.64	31±2.64	42±3.65	46±4.57	60±1.79
120	40±2.86	38±4.54	33±1.75	46±1.44	55±2.65	63±4.13

Mean ± SD, n=3

Ex vivo Mucoadhesion Time and Mucoadhesive Strength: The results of mucoadhesion study were presented in Table 5. The selected formulations were studied for ex vivo mucoadhesion time and the duration of mucoadhesion time was found in between 109 to 126 min. This indicates the duration of attachment with mucous membrane and period of effective drug release. The ex vivo mucoadhesive force were measured in between 0.278 to 0.479 Kg.m.s^{-2}. The formulation FAP14 showed highest mucoadhesive force of 0.479 Kg.m.s^{-2}.

Table 5: Ex vivo Mucoadhesion time and Ex vivo mucoadhesive strength of buccal patches of Atorvastatin

Formulation code	Ex vivo mucoadhesion time (min)	Ex vivo mucoadhesive strength (g)	Ex vivo mucoadhesive force (Kg.m.s-2)
FAP1	112 ± 4.64	34.87±1.22	0.341
FAP2	110 ± 2.54	32.81±0.45	0.321
FAP8	109 ± 3.75	28.37±2.51	0.278
FAP10	120 ± 3.85	39.84±2.01	0.390
FAP14	126 ± 3.64	48.92±0.38	0.479
FAP16	122 ± 4.54	42.43±0.11	0.416

In vitro Drug Release Kinetic Study: The kinetics of drug release was determined by fitting the in vitro release data with various models. The order of release followed by the formulation matrix was confirmed by the value of R^2, k' and 'n'. The formulation FAP1, FAP2, FAP8, FAP10 and FAP14 confirmed best match to the Higuchi model of drug release mechanism with high R^2 value of 0.9722, 0.9515, 0.9549, 0.9416 and 0.9217 respectively. These results confirmed the diffusion is the predominant mechanism of drug release from the above atorvastatin buccal patches. On the other hand the formulation FAP16 exhibited best match to the Korsmeyer-Peppas model by holding high R^2 value of 0.8665 and the release mechanism was found to be non-fickian principles. It was confirmed by the value of release exponent 'n' value of 0.8676. The variation in drug release was found as per the prediction of power law. This might be the result of simultaneous erosion and diffusion during drug release from formulations.

Table 6: R^2, K and n values of buccal patches

Formulations	Zero order		First order		Higuchi Korsmeyer		Peppas Model		Mechanism of drug release
	R^2	K_0	R^2	K_1	R^2	K	R^2 (min-1/2)	N	
FAP1	0.87	0.6188	0.5487	0.01	0.9722	8.5446	0.9384	0.9571	Diffusion
FAP2	0.8282	0.5914	0.5182	0.0095	0.9515	8.1618	0.9328	0.9319	Diffusion
FAP8	0.7768	0.6699	0.5223	0.0102	0.9549	8.2277	0.925	0.989	Diffusion
FAP10	0.8457	0.6443	0.471	0.0086	0.9416	9.268	0.9102	0.8769	Diffusion
FAP14	0.7598	0.6491	0.4317	0.0084	0.9217	9.1504	0.8938	0.8826	Diffusion
FAP16	0.6675	0.6318	0.3871	0.0079	0.8642	9.1999	0.8665	0.8676	Non-fickian release

Ex vivo permeation study: The permeation character of selected HPMC and PVA based atorvastatin buccal patches is shown in Table 7. The percentage of drug permeated across porcine buccal mucosa was found to be maximum of 98.99% for the formulation FAP16 at 60 min of study. Subsequently formulation FAP14 exhibited maximum release at 150 min, formulation FAP8 at 90 min, formulation FAP10 at 120 min and FAP1 and FA2 at 120 min of study. The satisfactory results were identified based on the duration to reach maximum drug permeation. The formulations reaching maximum drug release within their mucoadhesion time which was estimated earlier are selected for further study.

Table 7. The permeation characters of atorvastatin buccal patches

Time (min)	Percentage of drug permeated (%)*					
0	0	0	0	0	0	0
5	1.9±2.4	3.1±3.6	1.9±3.4	6.2±1.2	7.1±2.3	11.9±2.1
10	16.6±2.9	14.8±4.1	12.8±2.2	24.8±3.3	32.6±4.1	29.6±0.7
15	28.3±3.1	26.5±1.7	23.6±2.2	34.1±1.7	41.3±2.8	51.9±1.9
30	33.6±2.3	41.1±3.2	47.3±1.6	41.5±2.5	62.5±2.2	67.5±4.1
45	44.4±0.6	58.4±1.3	67.3±1.1	59.8±2.2	75.1±1.1	86.1±3.4
60	56.1±1.2	62.8±2.6	85.9±4.1	77.3±1.2	83.7±2.4	97.8±1.2
90	68.6±2.3	67±2.7	94.1±0.9	88.1±3.2	95.2±3.4	98.7±2.8
120	79.2±2.9	78.1±3.1	93±2.6	90±3.1	94.1±3.2	98.2±4.3
140	82.6±3.4	82±1.9	92±2.2	94.4±2.9	97±1.7	99.8±2.8

Accelerated Stability Studies: The stability of formulations was assessed at accelerated conditions of temperature and humidity of 40 ± 2ºC and 75±5% as per ICH guidelines. The evaluated parameters after exposure to such accelerated conditions were given in Table 8. The drug content of the patches showed slight variation in the range between 18.4 ± 0.4 and 19.9 ± 0.4 mg among tested formulations. Ex vivo Mucoadhesion time of patches also varied between 101±2.1 to 125±1.3 min.

Table 8: Accelerated stability studies data of Atorvastatin patches

Evaluation Parameters	Formulation code	1st month	2nd month	3rd month
Drug content (mg)	FAP1	18.8 ± 0.5	18.8 ± 0.2	18.8 ± 0.7
	FAP2	19.1 ± 0.6	19.2 ± 0.1	19.0 ± 0.3
	FAP8	19.2 ± 0.1	19.4 ± 0.5	19.5 ± 0.1
	FAP10	19.4 ± 0.4	18.7 ± 0.6	18.6 ± 0.5
	FAP14	19.3 ± 0.7	19.8 ± 0.4	19.6± 0.7
	FAP16	19.3 ± 0.4	19.6 ± 0.4	19.2 ± 0.1
Ex vivo mucoadhesion time (min)	FAP1	108 ± 2.3	107 ± 4	106 ± 2.1
	FAP2	104 ± 1.3	102 ± 0.5	102 ± 2.2
	FAP8	118 ± 3.2	114 ± 0.6	113 ± 2.4
	FAP10	115 ± 3.7	113 ± 1.8	112 ± 2.1
	FAP14	123 ± 2.4	121 ± 3.8	120 ± 2.3
	FAP16	129 ± 2.9	127 ± 4.1	126 ± 3.4

CONCLUSION

The present study mainly focused to formulate a buccal mucoadhesive drug delivery system for the delivery of atorvastatin. During this study an attempt was made to formulate mucoadhesive buccal patches of atorvastatin by solvent casting technique using various combinations of mucoadhesive polymers. The polymers used for the study were selected based on mucoadhesive property as it was reported in previous studies. Mucoadhesive polymers hydroxypropyl methylcellulose, polyvinyl alcohol, Ethyl cellulose, polyvinyl pyrrolidone were used in three different combinations and various proportions. Effect of permeation enhancers on the permeability of atorvastatin was also studied by using different permeation enhancers. These novel unidirectional buccal patches can be considered as alternative to oral route of administration of atorvastatin. This route may also provide additional advantages of bypassing the first pass metabolism and ease of administration for heart patients.

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