UPI Journal of Pharmaceutical Medical, and Health Sciences

Content Availabe at www.uniquepubinternational.com **ISSN: 2581-4532**

Research Article

Formulation and invivo evaluation of mucoadhesive buccal tablet of fluvastatin sodium

Raja Sekhar Reddy Poonuru*[1], Abdul Rasheed Ahmed[2], Rohini Cheruku[2], Pavan Juluri[2], Swetha Sreeramula[2], Akhila Madapu[2], Nethi Harika[2]

[1]Principal and Head, St.Peter's Institute of Pharmaceutical Sciences, Hanamkonda, PIN – 506001, Telangana, India

[2]Students, St.Peter's Institute of Pharmaceutical Sciences, Hanamkonda, PIN – 506001, Telangana, India

Article History

Received on: 15-04-2019
Revised on : 28-04-2020
Accepted on : 05-06-2020

Keywords

Buccal Delivery, Fluvastatin Sodium, Bio adhesion.

***Corresponding Author**

Raja Sekhar Reddy Poonuru
Email: yuppieraj@gmail.com

https://doi.org/10.37022/jpmhs.v3i2.22

Abstract

The main objective of this work is to develop mucoadhesive tablet of Fluvastatin sodium, is a sodium salt of a synthetic lipid-lowering agent with potential anti neoplastic activity by employing natural and synthetic polymer and overcome bioavailability related problems and also reduce frequency of administration. Buccal tablets were prepared using HPMC K4M, K15M and Xanthum gum for release retardation, Carbopol 934 for bio adhesion and Chitosan for permeation enhancement. Ethyl cellulose was utilised for backing membrane. It was observed that the release rate slowed down with increasing concentration of carbopol 934 and release rate increased with carbopol 934 and Na CMC from 1:1 to 1:2 ratios in F16 to F 20.NaCMC containing formulations showed better bio adhesion than the HPMC K4M & Carbopol 934.

Introduction

Systemic trans mucosal delivery of therapeutic agents via the mucosal epithelium lining of accessible body cavities, such as oral cavity (Buccal),nose (nasal), rectum (rectal), and vagina (vaginal) have received renewed interest within last two decades. These routes have numerous advantages over per oral drug delivery, such as bypassing hepatic first-pass clearance, and therefore potentially improving systemic bioavailability [1-5].

Materials And Methods

Preparation of bilayered buccal tablets Bilayered buccal tablets of Fluvastatin sodium were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.60, except lubricant all the ingredients were thoroughly blended in a glass mortar with pestle for 15 min. After sufficient mixing lubricant was added and again mixed for additional 2-3 min.Preparation involves two steps, first the mixture is compressed using 8 mm flat faced punch on 16 stages rotary tablet compression machine. Then upper punch is raised and the backing layer of ethyl cellulose is placed on above compact then two layers are compressed again to get bi layered buccal tablet [6-8]. Composition of the prepared bio adhesive buccal tablets is given in Table 1 and Table 2.

Tab1: Composition of formulations containing chitosan: HPMC K4M &xanthangum: HPMC K4M \ K15M using different diluents

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ingredients(mg/tablet)	1:1	1:2	2:1	3:1	1:1	1:2	2:1	3:1	1:1	1:2	2:1	3:1
Fluvastatin sodium	40	40	40	40	40	40	40	40	40	40	40	40

Chitosan	30	20	40	45	-	-	-	-	-	-	-	-
HPMC K4M	30	40	20	15	30	40	20	15	-	-	-	-
Xanthan Gum	-	-	-	-	30	20	40	45	30	20	40	45
HPMC K15M	-	-	-	-	-	-	-	-	30	40	20	15
Lactopress SD 250	-	-	-	-	40	40	40	40	40	40	40	40
MCC	40	40	40	40	-	-	-	-	-	-	-	-
Aspartame	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	10	10	10	10	10	10	10	10	10	10	10	10
Backing Layer Ethyl cellulose Mg Stearate	35 10	35 10	35 10	35 10	35 10	35 10	35 10	35 10	35 10	35 10	35 10	35 10
Total weight(mg)	200	200	200	200	200	200	200	200	200	200	200	200

Tab 2: Composition of formulations containing carbopol-934: HPMC K4M &Carbopol-934:NaCMC in different ratio's

Formulation code	**F 13**	**F 14**	**F 15**	**F 16**	**F 17**	**F 18**	**F 19**	**F 20**
Ingredients(mg/tablet)	**1:1**	**1:2**	**2:1**	**3:1**	**1:1**	**1:2**	**2:1**	**3:1**
Fluvastatin sodium	40	40	40	40	40	40	40	40
Carbopol-934	30	20	40	45	30	20	40	45
HPMC K4M	30	40	20	15	-	-	-	-
NaCMC	-	-	-	-	30	40	20	15
Lactopress SD 250	40	40	40	40	40	40	40	40
Aspartame	5	5	5	5	5	5	5	5
Magnesium stearate	10	10	10	10	10	10	10	10
Backing Layer Ethyl cellulose Mg Stearate	35 10	35 10	35 10	35 10	35 10	35 10	35 10	35 10
Total weight (mg)	200	200	200	200	200	200	200	200

Evaluation Of Buccal Tablets

Thickness

The thickness of buccal tablets was determined using digital micrometer. Ten individual tablets from each batch were used and the average was taken out of the results [9].

Weight variation test

Weight variation was performed for 20 tablets from each batch using an electronic balance and average values were calculated [10].

Hardness

Hardness was conducted for 3 tablets from each batch using Monsanto hardness tester and average values were calculated [11].

Assay

Ten tablets were weighed and grounded in a mortar with pestle to get fine powder; powder equivalent to the mass of one tablet was dissolved in methanol by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 239 nm using an UV spectrophotometer [12].

Measurement of bio adhesion strength

Bioadhesive strength of the tablets was measured on a modified physical balance.The apparatus consisted of a modified double beam physical balance in which a lighter pan had replaced the right pan and the left pan had been replaced by a glass slide (4 cm length and 2.5 cm width) with plastic hang suspended by Teflon rings and copper wire. The left-hand side of the balance was exactly 5 g heavier than the right side .The height of the total set up was adjusted to accommodate a glass container of 6.6 cm height. The sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8, at 37°C ± 1°C) so that it just touched the mucosal surface. In order to find out the bio adhesion strength first buccal tablet (n=3) was stacked to the lower side of rubber stopper with cyanoacrylate adhesive. Two sides of the balance made equal by keeping 5 gm. weight in the right pan.Now five grams weight from the right pan was then removed. This lowered the glass slide along with the tablet over the mucosal membrane with a weight of 5.0 g. This was kept undisturbed for 5 min. Then the weights on the right-hand

side were slowly added in increments of 0.1 g till the tablet just separated from the membrane surface. The excess weight on the right pan, *i.e*. total weight minus 5grams was taken as a measure of the bioadhesive strength [13].

Bio adhesion strength = Weights added – 5 grams weight

Determination of the *ex vivo* residence time

The *ex vivo* residence time was determined using a locally modified USP disintegration apparatus as reported by Nakumara et al., The medium was composed of 800 ml of phosphate buffer pH 6.8 maintained at 37⁰ C. A segment of sheep buccal mucosa of 3 cm length was glued to glass slab. The tablet surface was hydrated using phosphate buffer pH 6.8 and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the tablet was completely immersed into the buffer solution at the lowest point and was out at the highest point.The time necessary for complete erosion or detachment of tablet from mucosal surface was recorded.

Swelling Studies

Buccal tablets were weighed individually (designated as W_1) and placed separately in Petri dishes containing 15 mL of phosphate buffer (pH 6.6) solution. At regular intervals (1, 2, 3, 4, 5, 6, 7 and 8 h), the buccal tablets were removed from the petri dishes and excess surface water was removed carefully using the filter paper. The swollen tablets were then reweighed (W_2)**.** This experiment was performed in triplicate. The swelling index (water uptake) calculated according to the following Equation [14].

Swelling index = $(W_2\text{-}W_1) / W_1$

Surface pH Study

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The bioadhesive tablet was allowed to swell by keeping it in contact with 1 mL of distilled water for 2 hours at room temperature. The pH was measured by bringing the pH-meter electrode, in contact with the surface of the tablet and allowing it to equilibrate for 1 min [15].

In vitro drug release of buccal tablets

Stability of buccal tablets

The short term stability studieswas performed for optimized formulation (F18) as per ICH guide-lines for a period of 3 months. For this, ten tablets were individually wrapped using aluminum foil and packed in amber color screw cap bottle and put at above specified condition in incubator for 3 months. After each month tablet sample was analyzed for physical Characteristics.The tablets were periodically evaluated at regular time intervals (0, 2, 4, 6 and 8 h), the buccal tablets were examined for change in color, surface area and integrity. The experiments were repeated in triplicate (n = 3) in a similar manner [18].

Fourier transforms infrared spectroscopic studies

The United States Pharmacopeia (USP) XXIII rotating paddle method was used to study the drug release from the buccal tablets. The dissolution medium consisted of 500 mL of phosphate buffer pH 6.6. The release was performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm [12]. The backing layer of buccal tablet was attached to the glass slide with instant adhesive (cyanoacrylate adhesive). The slide was placed in to the bottom of the dissolution vessel. Samples (5 mL) were withdrawn at predetermined time intervals and replaced with fresh medium.The samples were filtered through filter paper and analyzed after appropriate dilution by UV spectrophotometer at 239 nm [16].

***Ex vivo* permeation of buccal tablets**

Ex vivo permeation study using sheep buccal mucosa was performed using Franz diffusion cell at 37 ± 0.2°C. This temperature and rpm was maintained by using magnetic stirrer. The epithelium was separated from underlying connective tissues with surgical scissors and clamped between donor and receiver chambers of the Franz-type diffusion cell. After the buccal membrane was equilibrated for 30 min with Krebs buffer solution between both the chambers, the receiver chamber was filled (25 ml) with fresh pH 7.4 buffer solution The buccal tablet was placed in donor chamber and 1mL of buffer solution (pH 6.6) was added and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 50 rpm.Aliquots (2 mL) were collected at predetermined time intervals and filtered andafter appropriate dilution with isotonic phosphate buffer pH 7.4, the amount of drug permeated through the buccal mucosa was then determined by measuring the absorbance at 239 nm using a UV spectrophotometer. The medium of the same volume (2 mL), which was prewarmed at 37°C, was then replaced into the receiver chamber. The experiments were performed in triplicate (n = 3) and mean value was used to calculate the amount of drug permeated [17].

Amount permeated =concentration * dilution factor * 25ml

% drug release = amount permeated/dose * 100

FTIR spectroscopic studies were conducted for optimized formulation, Carbopol-934 and Fluvastatin sodium pure drug. The samples were analyzed between wave numbers 4000 and 600 cm^{-1}.

Results

Tab 3: Physicochemical parameters of mucoadhesive buccal tablets of Fluvastatin (F1 to F12)

Formulation code	Thickness (mm)	Weight Variation(mg)	Friability (%)	Hardness (Kg/cm²)	%Drug content
F1	3.43 ± 0.010	201.0 ± 0.47	0.09 ± 0.05	4.3 ± 0.13	88.74

F2	3.26 ± 0.020	200.2 ± 0.72	0.17 ± 0.02	4.8 ± 0.33	74.17
F3	2.73 ± 0.035	200.5 ± 0.52	0.08 ± 0.02	5.3 ± 0.13	86.69
F4	3.64 ± 0.010	201.4 ± 0.34	0.07 ± 0.05	5.6 ± 0.10	82.04
F5	3.64 ± 0.040	200.8 ± 0.51	0.24 ± 0.07	4.6 ± 0.10	80.58
F6	2.91 ± 0.030	201.5 ± 0.34	0.31 ± 0.01	5.1 ± 0.05	75.39
F7	2.90 ± 0.010	201.7 ±0.37	0.42 ± 0.04	5.5 ± 0.05	89.57
F8	3.54 ± 0.030	204.0 ± 0.22	0.08 ± 0.01	5.7 ± 0.05	82.07
F9	3.71 ± 0.042	201.6 ± 0.31	0.08 ± 0.03	3.9 ± 0.09	89.40
F10	3.38 ± 0.057	199.8 ± 0.65	0.42 ± 0.02	4.9 ± 0.15	74.37
F11	3.36 ± 0.023	201.1 ± 0.57	0.08 ± 0.02	4.7 ± 0.21	85.38
F12	3.55 ± 0.010	200.9 ± 0.53	0.46 ± 0.03	5.6 ± 0.10	88.03

Tab 4: Physicochemical parameters of mucoadhesive buccal tablets of Fluvastatin(F13 to F20)

Formulation code	Thickness (mm)	Weight Variation(mg)	Friability (%)	Hardness (Kg/cm²)	%Drug content
F13	3.64 ± 0.024	198.1 ± 0.50	0.12 ± 0.02	5.0 ± 0.05	84.94
F14	3.64 ± 0.110	199.2 ± 0.30	0.42 ± 0.05	4.5 ± 0.08	82.75
F15	2.99 ± 0.020	200.0 ± 0.35	0.08 ± 0.04	4.4 ± 0.12	79.66
F16	2.91 ± 0.024	192.8 ± 0.25	0.06 ± 0.02	5.5 ± 0.10	75.62
F17	3.61 ± 0.032	198.8 ± 0.55	0.12 ± 0.03	4.8 ± 0.08	84.75
F18	3.35 ± 0.030	202.3 ± 0.50	0.25 ± 0.01	4.5 ± 0.21	89.16
F19	3.54 ± 0.005	197.3 ± 0.30	0.31 ± 0.01	4.7 ± 0.04	88.98
F20	3.66 ± 0.020	195.9 ± 0.45	0.24 ± 0.08	5.5 ± 0.14	84.11

Tab 5: The bioadhesive strength, *ex vivo* residence time and surface pH dataof (F1 to F12)

Formulation code	Bio adhesion Strength (gm.)	*Ex vivo* residence time(hr)	Surface pH
F1	21.2 ± 0.08	4.62 ± 0.10	5.91 ± 0.010
F2	16.1 ± 0.15	4.41 ± 0.15	6.40 ± 0.515
F3	31.1 ± 0.10	6.52 ± 0.25	6.21 ± 0.015
F4	28.8 ± 0.28	5.33 ± 0.15	6.66 ± 0.515
F5	19.4 ± 0.21	4.73 ± 0.10	6.13 ± 0.010
F6	21 ± 0.06	5.15 ± 0.35	6.85 ± 0.015
F7	28.3 ± 0.27	6.74 ± 0.14	6.81 ± 0.035
F8	30.6 ± 0.06	5.57 ± 0.25	6.85 ± 0.005
F9	18.5 ± 0.31	5.13 ± 0.35	6.75 ± 0.010
F10	20.3 ± 0.07	5.35 ± 0.27	6.91 ± 0.040
F11	25.5 ± 0.16	6.26 ± 0.31	6.63 ± 0.050
F12	30.1 ± 0.19	6.45 ± 0.16	6.92 ± 0.015

Tab 6: The bioadhesive strength, *ex vivo* residence time and surface pH data of (F13 to F20)

Formulation code	Bio adhesion Strength (gm.)	Ex vivo residence time(hr)	Surface pH
F13	17.2 ± 0.09	4.75 ± 0.20	6.81 ± 0.050
F14	18.2 ± 0.05	4.25 ± 0.30	7.05 ± 0.070
F15	15.1 ± 0.14	5.82 ± 0.10	6.33 ± 0.050
F16	20.4 ± 0.04	6.30 ± 0.20	6.86 ± 0.005
F17	28.8 ± 0.13	6.35 ± 0.25	6.84 ± 0.020
F18	32.2 ± 0.24	6.85 ± 0.15	6.89 ± 0.025
F19	22.5 ± 0.08	6.25 ± 0.35	7.05 ± 0.085
F20	24.8 ± 0.24	6.55 ± 0.43	5.99 ± 0.010

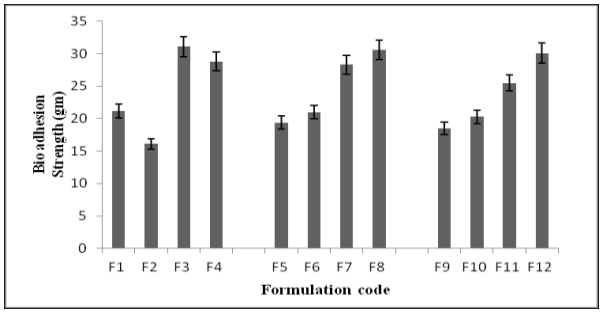

Fig 1: Bio adhesion profile of mucoadhesive buccal tablets of Fluvastatin (F1 to F12)

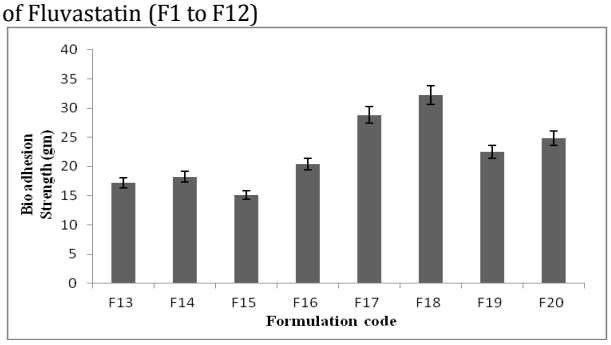

Fig 2: Bio adhesion profile of mucoadhesive buccal tablets of Fluvastatin(F13 to F20)

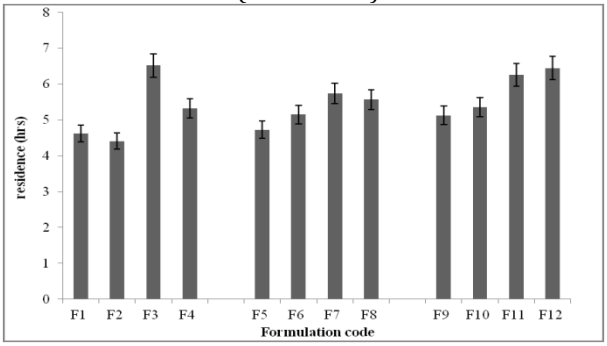

Fig 3: *Ex vivo* residence profile of mucoadhesive buccal tablets of Fluvastatin(F1 to F12)

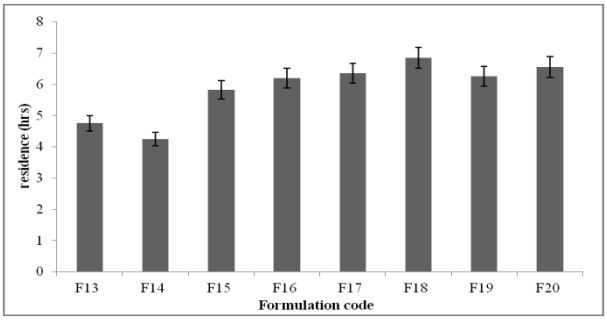

Fig 4: *Ex vivo* residence profile of mucoadhesive buccal tablet of Fluvastatin(F13 to F20)

Measurement Of Bio Adhesion Strength

This evaluation test was conducted for all formulations; there is a gradual increase in bio adhesion strength from F1to F4. The maximum bio adhesion strength (31.1 g, 32.2 g) was found for formulations F3, F18 and low bio adhesion strength was found for F15, F2 (15.1g ,16.1). Bio adhesion is defined as the attachment of a synthetic or natural macromolecule to mucus and/or an epithelial surface (Longer and Robinson, 1986). Muco adhesion is considered to occur in four major stages wetting, interpenetration, adsorption and formation of secondary chemical bonds between mucus membrane and polymers. The mucoadhesive strength is affected by molecular weight of polymer, contact time with mucus and degree of swelling of the polymer (Park *et al.,* 1987). The bilayered tablets containing higher proportions of carbopol showed good bio adhesion strength for 5min contact time. Bio adhesion characteristics were found to be affected by the nature and proportion of bioadhesive polymers used. As the concentration of carbopol increased the bioadhesive strength was also increased, the reason for such findings might be ionization of CP at salivary pH, which leads to the formation of secondary bio adhesion bonds with mucin and interpenetration of the polymer chains in the interfacial region, while other polymers undergo superficial bio adhesion. The optimized tablet (F18) showed 32.2 ± 0.24 g of bio adhesion strength. Bio adhesion strength values of all the formulations represented in Table 12.1, 12.2 andcomparison of bio adhesion strength of all formulations was shown in figure 7.1 and 7.2.

Ex vivo residence time

Ex vivo residence time for all the formulations varied from 4.25 - 6.85 h. The optimized formulation (F18) showed 6.85±0.15 h. The difference could be due to the combination of various amounts of polymers, which affects the mucoadhesion. In fact with bilayered tablets containing higher proportion of carbopol the mucoadhesion time was found to be increased. This is because of the high mucoadhesive nature of the carbopol and inter penetration of polymeric chains in to the mucus membrane. *Exvivo* residence time and bio adhesion strength values were given

in Table 12. The maximum *ex vivo* residence time (6.74 h, 6.85 h) was found for formulations F7, F18 and low *ex vivo* residence time was found for formulations F2 (4.41 h), F14 (4.25 h) .

Surface pH Study of buccal tablets

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. The surface pHfor all the buccal tablets was from 5.91 to 7.05 which was nearer to salivary pH (6.5-7.5), so the formulation does not cause any mucosal irritation and discomfort.

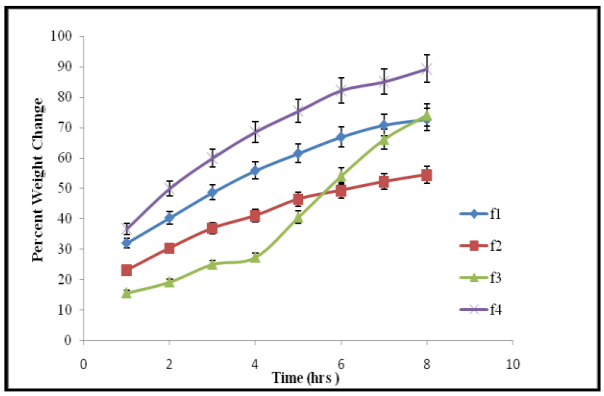

Fig 5: Swelling index profile of formulations containing xanthan chitosan

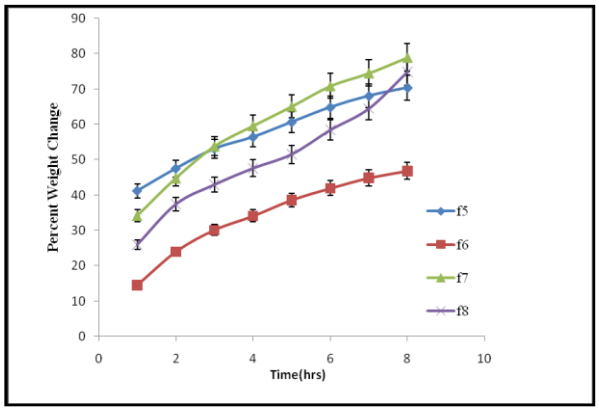

Fig 6: Swelling index profile of formulations containing & HPMC K4M gum & HPMC K4M

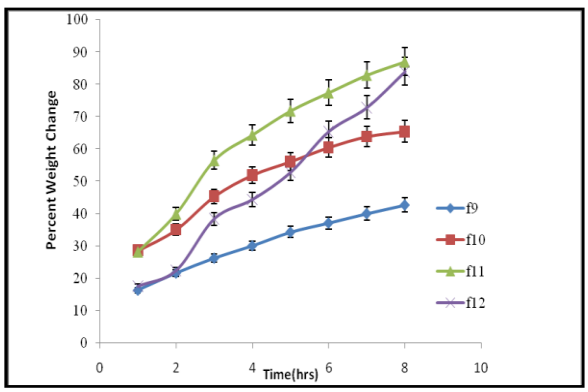

Fig 7: Swelling index profile of formulations containing xanthan gum & HPMC K15M

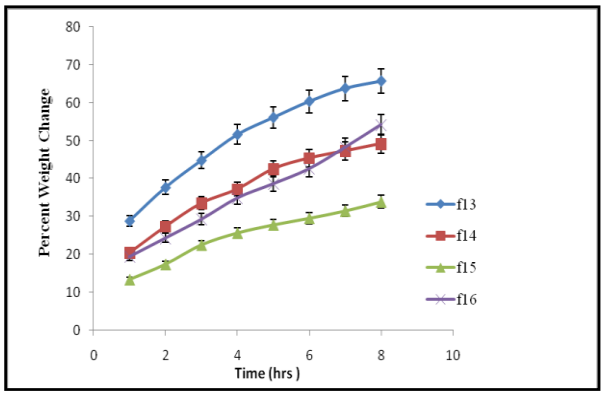

Fig 8: Swelling index profile of formulations containing carbopol & HPMC K4M

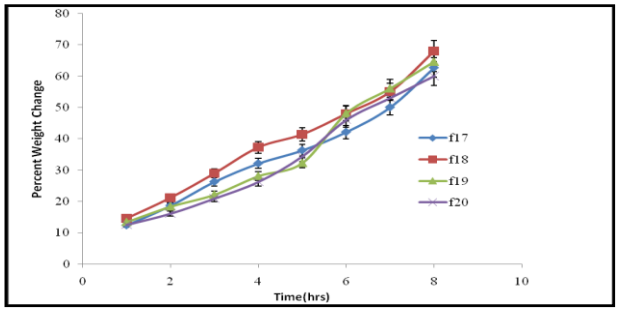

Fig 9: Swelling index profile of formulations containing carbopol & NaCMC

Swelling Studies Of Buccal Tablets

The chitosan isinsoluble in aqueous media of pH 6.6 but absorbs large quantity of water and hence gets swelled. The swelling was getting affected in the formulations containing secondary polymer along with chitosan as a primary polymer. The highest swelling of 85.07 to 89.31% for formulations (F4) which contains chitosan: HPMC K4M in 3:1 ratio with spray dried lactose as diluent. Formulations with spray dried lactose showed higher swelling index values compared to MCC, this is because of the water soluble diluents (spray dried lactose) can absorb more water and swell higher extents than that of water insoluble diluent (MCC). The swelling index for the formulations containing xanthan gum and HPMC K15M was less (F10-87.08) compared to chitosan due to formation of highly viscous mucilaginous layer over the surface of the tablet.In formulations containingCarbopol: HPMC K4M (F16) shows swelling index of 54.20; within the formulations containing (F17 to F20) shows swelling index of 62.76,68.06,64.76 &60.06; within the formulations, the optimized formulation (F18) shows swelling index 68.06 ± 0.23. The swelling index is directly proportional to carbopol content and inversely proportional to cellulose polymers, it was found that the amount of carbopol plays an important role in swelling of the matrix and leads to the drug diffusion. It was observed that swelling rate increased with an increase in carbopol polymer content of the prepared tablets.

Release kinetics and mechanism

Observation of all the r^2 values indicated that the highest r^2 (0.9972) value was found for Zero order release. According to 'n' value it is greater than one, so it follows supercase II transport with zero order release.In super case II, in addition to diffusion, other release mechanism includingmatrix erosion and polymer relaxation mightbe involved.

Tab 7: Release kinetics and mechanism of optimized formulation

Formulation code	Mathematical models (Kinetics)				
	Zero order	First order	Higuchi	Peppas model	
	r^2	r^2	r^2	n	r^2
18	0.9972	0.9467	0.983	1.0449	0.9978

***Ex vivo* permeation of buccal tablets**

Based on the *in vitro* drug release studies, F7, F12, F16, F18 was selected for the *ex vivo* permeation study. The oral mucosa of sheep resembles that of humans more closely in terms of structure and composition, therefore sheep buccal mucosawas selected for permeation studies. The drug Fluvastatin sodium is a highly water soluble with low "log p" value falls in BCS II category. The values of cumulative amount of drug permeated and cumulative percent drug permeated were as shown in Figure 15.

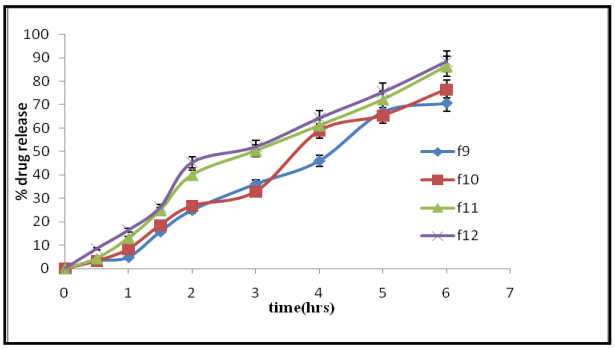

Fig 10: Comparison of In vitro release profile of Fluvastatin sodiummu coadhesive buccal tablets using two different diluents

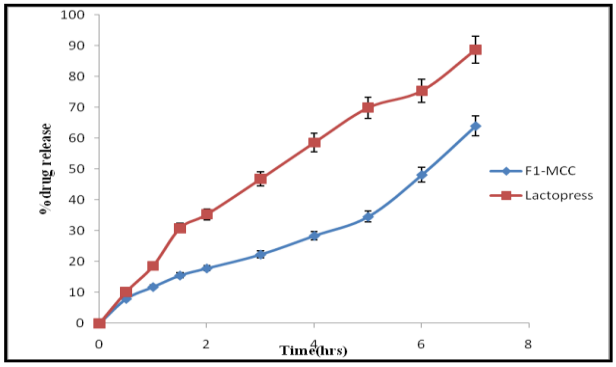

Fig 11: *In vitro* cumulative percentage drug release Profile of Fluvastatin Sodium from mucoadhesive buccal tablets containing xanthan gum & HPMC K4M

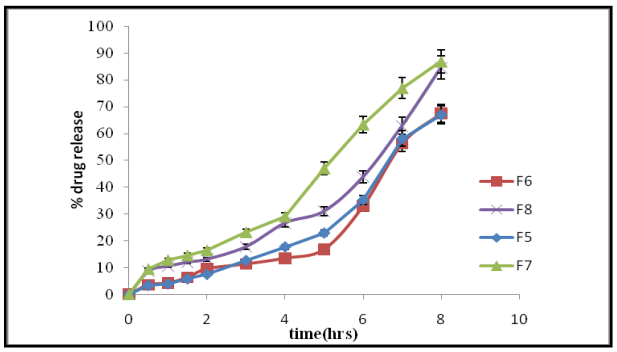

Fig 12: *In vitro* cumulative percentage drug release profile of Fluvastatin Sodium from mucoadhesive buccal tablets containing xanthan gum & HPMC K15M

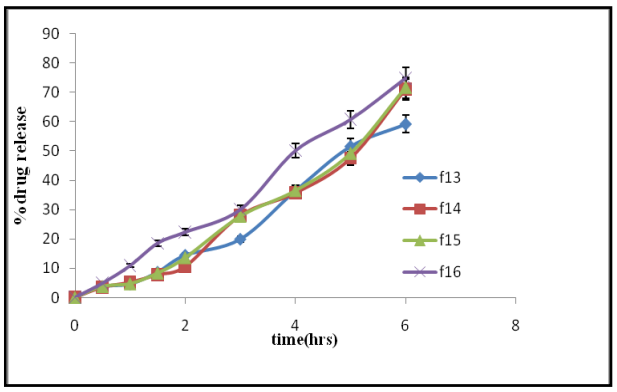

Fig 13: *In vitro* cumulative percentage drug release profile of Fluvastatin Sodium from mucoadhesive buccal tablets containing carbopol 934 &HPMC K4M

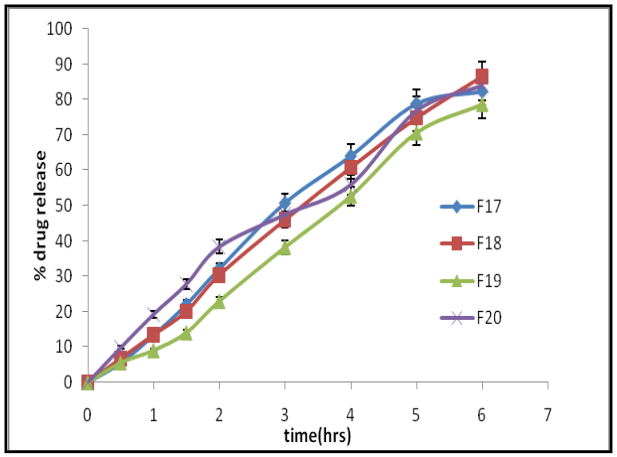

Fig 14: *In vitro* cumulative percentage drug release profile of Fluvastatin Sodium from mucoadhesive buccal tablets containing carbopol 934 &NaCMC

***In vitro* drug release of buccal tablets**

An ideal controlled release system should be able to release the drug immediately to attain the therapeutic level at a faster rate and maintain this drug level for a prolonged period of time(Lopez *et al.,* 1998)**.** *In vitro* drug release studies revealed that the release of Fluvastatin sodium from different formulations varies with

characteristics and composition of matrix forming polymers as shown in graphs. The release rate of Fluvastatinsodium decreased with increasing concentration of HPMC K4M , HPMC K15M in F6 (67.44 ± 0.21%) , F10 (76.54 ± 0.18%), and F14 (70.96 ± 0.34 %) respectively. The buccal tablets containing chitosan along with HPMC K4M showed drug release of 88.67 ± 0.18 in 7 hrs using spray dried lactose as diluents.As the amount of xanthan gum in the matrix increased, there would be a greater degree of hydration with simultaneous swelling which results in a lengthening of the drug diffusion pathway and reduction in drug release rate (88.55 ± 0.06) in F12.

The release rate of Fluvastatin increased with decreased carbopol 934 and increasing concentration of NaCMC in F18 (CP:NaCMC in 1:2). The most important factor affecting the rate of release from the buccal tablets is the drug: polymer ratio. Carbopol 934P is more hydrophilic and has excellent mucoadhesive, gelling properties and also helps in sustaining

Release kinetics and mechanism

Observation of all the r^2 values indicated that the highest r^2 (0.9972) value was found for Zero order release. According to 'n' value it is greater than one, so it follows supercase II transport with zero order release.In super case II, in addition to diffusion, other release mechanism includingmatrix erosion and polymer relaxation mightbe involved.

Tab 7: Release kinetics and mechanism of optimized formulation

Formulation code	Mathematical models (Kinetics)				
	Zero order	First order	Higuchi	Peppas model	
	r^2	r^2	r^2	n	r^2
18	0.9972	0.9467	0.983	1.0449	0.9978

***Ex vivo* permeation of buccal tablets**

Based on the *in vitro* drug release studies, F7, F12, F16, F18 was selected for the *ex vivo* permeation study. The oral mucosa of sheep resembles that of humans more closely in terms of structure and composition, therefore sheep buccal mucosawas selected for permeation studies. The drug Fluvastatin sodium is a highly water soluble with low "log p" value falls in BCS II category. The values of cumulative amount of drug permeated and cumulative percent drug permeated were as shown in Figure 15.

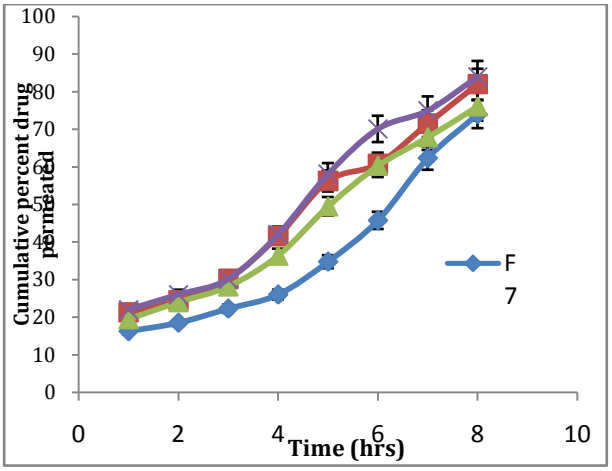

Fig 15: Cumulative percent drug permeation of selected Fluvastatin formulations

Stability of buccal tablets

Stability study was conducted only for optimized formulation (F18). There was no change in the colour and integrity of the tablets. The data obtained from the study presented in Table 8. From the stability results it was known that formulation F18 has stability in human saliva, if it is unstable color would change.Physical properties of the Fluvastatin sodium buccal tablets such as thickness and diameter slightly changed owing to swelling of the system in human saliva.

Tab 8: Stability profile of optimized formulation in human saliva

Sampling interval (h)	Change in colour	Change in surface area (cm^2)	Change in integrity
0	NO	NO	NO
2	NO	0.5	NO
4	NO	1.32	NO
6	NO	2	NO
8	NO	2.5	NO

Fourier transform infrared (FTIR) spectroscopic studies

FTIR spectra of drug and the optimized formulation were recorded in range of 4000-600cm^{-1}. FTIR spectra of pure Fluvastatin drug and polymer (carbopol 934) was compared with the FT-IR spectra of tablet powder ofoptimized formulation showed in the figure 11.1 to 11.3 respectively. The characteristic functional group of pure Fluvastatin sodium and polymer showed the peaks at the following wave region.FTIR spectra of pure drug shows the peaks at 1536cm^{-1} due to C=O stretching, 882.2 cm^{-1} due to aryl-F functional group, 3236cm^{-1} due to aryl-H, 2986 cm^{-1} due to C=C stretching, 3746 cm^{-1} due to O-H bending which are characteristic band for pure drug Fluvastatin Sodium.After complex with polymers, same pure drug considerable peak was observed from the drug polymer complex as shown in figure 16.

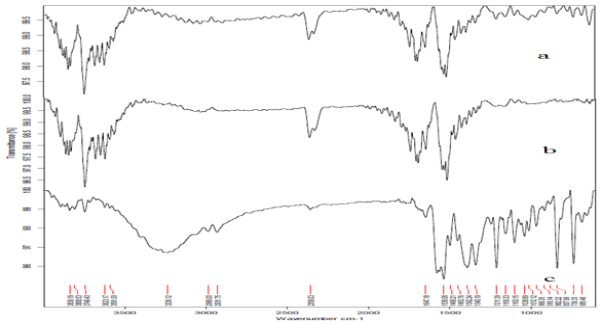

Fig 16: FTIR spectra for a) optimized formulation b) carbopol 934 c) Fluvastatinsodium pure drug

Conclusion

Development of bioadhesive buccal drug delivery of Fluvastatinsodium tablets is one of the alternative routes of administration to avoid first pass effect and provide prolongs release. A combination of carbopol 934 and Sodium carboxyl methyl cellulose at the ratio of 1:2 is with complementary physical properties. From the results, it was concluded that the *in vitro* drug release, bio adhesion strength, *ex vivo* residence time of the optimized formulation is suitable for buccal delivery. The release pattern followed non-fickian diffusion with Zero order release. The results strongly suggest that increase in cumulative drug permeated was due to effect of sodium tauroglycholate on paracellular and transcellular pathways. Formulation containing carbopol 934 and Sodium carboxyl methyl cellulose was found to be an optimized formulation, which could be useful for buccal administration of Fluvastatin may overcome the disadvantage of poor bioavailability. FTIR studies concluded that there was no interaction between drug and excipients. It concludes that buccal delivery of Fluvastatin sodium tablets can be good way to bypass the first-pass metabolism. It may render great bioavailability.

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