

## Formulation and evaluation of buccoadhesive quetiapine fumarate tablets

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The aim of present study was to develop and evaluate buccoadhesive Quetiapine Fumarate (QF) tablets, which is extensively metabolised by liver. Buccoadhesive tablets of QF were prepared using HPMC K4M, HPMC K15M and combination of carbopol and HPC as mucoadhesive polymers by direct compression method. Sodium deoxycholate was added to formulation to improve the permeation of drug. The formulations were tested for bioadhesion strength, *ex vivo* residence time, swelling time and *in vitro* dissolution studies and *ex vivo* permeation studies. Optimized formulation (F3) showed 92% *in vitro* release in 8 h and 67% permeation of drug through porcine buccal mucosa and followed fickian release mechanism with zero order kinetics. FTIR studies of optimized formulation showed no evidence of interaction between the drug and polymers. *In vivo* mucoadhesive behaviour of optimized formulation was performed and subjective parameters were evaluated.

**Uniterms:** Quetiapine Fumarate. Bioadhesion. *In vivo* mucoadhesive behaviour.

O objetivo do presente estudo foi desenvolver e avaliar os comprimidos bucoadesivos de fumarato de quetiapina (FQ), que é extensivamente metabolizada no fígado. Os comprimidos bucoadesivos de FQ foram preparados utilizando-se HPMC K4M, HPMC K15M e a combinação de carbopol e HPC como polímeros mucoadesivos pelo método de compressão direta. O desoxicolato de sódio foi adicionado à formulação para melhorar a permeação do fármaco. As formulações foram testadas quanto à força de bioadesão, tempo de residência *ex vivo*, tempo de inchamento, dissolução *in vitro* e permeação *ex vivo*. A formulação otimizada (F3) mostrou 92% de liberação *in vivo* em 8 h e 67% de permeação do fármaco através da mucosa bucal de porco e seguiu o mecanismo fickiano de liberação com cinética de ordem zero. Os estudos de FTIR da formulação otimizada não mostraram evidência da interação entre o fármaco e os polímeros. O comportamento mucoadesivo *in vivo* da formulação otimizada foi efetuado e avaliaram-se os parâmetros subjetivos.

**Uniterms:** Fumarato de quetiapina. Bioadesão. Comportamento mucoadesivo *in vivo*.

### INTRODUCTION

Bioadhesive buccal drug delivery provides an attractive alternative to the oral route of drug administration particularly overcoming deficiencies such as high first-pass metabolism and drug degradation in the harsh gastrointestinal environment (Gibaldi, 1985; Senel, Hincal, 2001). The stratified squamous epithelium supported by a connective tissue lamina of buccal mucosa was targeted as

a site for drug delivery (Squier, Wertz, 1996). Buccal drug delivery provides a number of advantages like robustness of epithelium, usage of the dosage form in accordance with need, good accessibility and comparatively less susceptibility to enzymatic activity (Shanker *et al.*, 2009) and can administer drugs to patient who cannot be dosed orally to prevent accidental swallowing (Vamshi Vishnu *et al.*, 2007). Therefore, adhesive mucosal dosage forms were developed for oral delivery, in the form of adhesive tablets (Schor *et al.*, 1983; Owens, Dansereau, Sakr, 2005; Akbari *et al.*, 2004), adhesive gels (Bremecker, Stempel, Klein, 1984; Ishida, Vambu, Vagai, 1983; Packer *et al.*, 2001) and adhesive patches (Guo, 1994; Anders, Merkle, 1989).

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The major limiting factor for development of Bioadhesive buccal delivery devices is the permeation of drug through membrane. The main barrier for the absorption of drug is the epithelium of the buccal mucosa. To improve absorption through buccal mucosa, several approaches have been investigated. By changing the physicochemical properties of the drug, increased permeation of the drug through the buccal membrane and prevention of drug degradation by enzyme was achieved (Shojaei, 1998). The amount of drug available for absorption was increased by improving the bioadhesion and release characteristics of buccal delivery (Nagai, Machida, 1985). Addition of permeation enhancers is one of the approaches. Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. Incorporation of permeation enhancers improves the delivery of drug via buccal membrane, which could reduce barrier properties of the buccal epithelium (Aungst, Rogers, 1989; Lee, Yamamoto, Kompella, 1991; Pitha, Harman, Michel, 1986; Burnside, Keith, Snipes, 1989; Zhang *et al.*, 1994; Steward, Bayley, Howes, 1994; Ebert *et al.*, 1994; Hoogstraate *et al.*, 1997).

Quetiapine Fumarate (QF), 2-[2-(4-dibenzo [*b, f*] [1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1) (salt), is an atypical psychotropic agent belonging to a class dibenzothiazepine derivate. It is used in the treatment of schizophrenia and manic episode associated with bipolar I disorder (Bhanudas, Sanjay, 2009). The peak plasma concentration is reached with in 1.5h. The bioavailability of QF is about 9% and half life is 6 hr and is widely distributed through out the body and 83% of drug binds to plasma proteins. It is extensively metabolised in liver to the sulfoxide metabolite and parent acid metabolite by sulfoxidation and oxidation; both metabolites are pharmacologically inactive leading to lower bioavailability. So, QF is selected as model drug for Bioadhesive buccal drug delivery to overcome extensive first-pass metabolism.

The aim of present study was to develop buccoadhesive QF tablets to enhance bioavailability of drug.

## MATERIAL AND METHODS

### Material

Quetiapine Fumarate (QF) is a gift sample from Matrix Laboratories, Hyderabad, India. Hydroxypropyl methylcellulose (HPMC K4M, HPMC K15M) and perlitol S.D. 200 are gift samples from Dr. Reddy's Laboratories, Hyderabad. Carbopol 934P was purchased from S. D. Fine Chem. Ltd., Mumbai, India. Hydroxy propyl cellulose (HPC) was donated by Natco Pharma, Hyderabad, India. Sodium deoxycholate was purchased from Moly Chem.,

Mumbai, India. All other chemicals and reagents used were of analytical grade.

### Methods

#### *Solubility studies*

Quetiapine Fumarate (QF) solubility studies in phosphate buffer, pH 6.6 was determined by phase equilibrium method. An excess amount of QF was taken in 20 mL vial containing 10 mL of phosphate buffer, pH 6.6. These vials were closed with rubber caps and agitated at room temperature for 24 h using rotary shaker (Remi Instruments, Mumbai, India). The solution was filtered through a 0.2  $\mu\text{m}$  whatman filter paper after 24 h. The amount of drug solubilized was estimated by measuring absorbance at 250 nm using a UV spectrophotometer (Systronic PC-Based Double Beam Spectrophotometer 2202, Ahmedabad, India) (Gupta, Garg, Khar, 1993). The studies were repeated in triplicate ( $n=3$ ) and mean was calculated.

#### *Tissue isolation*

Buccal tissue of domestic pork was taken from a local slaughter house and was stored in Krebs buffer, pH 7.4 at 4 °C upon collection. The epithelium was separated from the underlying connective tissue with a surgical procedure. The membrane was mounted within 24 h of isolation of buccal tissue over Franz diffusion cell.

#### *Ex vivo permeation of drug solution*

*Ex vivo* permeation of drug solution through the porcine buccal membrane was studied. The buccal epithelium was carefully mounted over a Franz diffusion cell with an internal diameter of 2.4 cm (4.52 cm<sup>2</sup> area) and with a receptor compartment volume of 14 mL. It is filled with phosphate buffer, pH 6.6. After the buccal membrane was equilibrated for 30 min with buffer solution, the receptor chamber was filled with fresh phosphate buffer solution (pH 6.6) and the donor chamber was charged with (5 mL) buffer solution. The entire setup was placed over magnetic stirrer (Remi, 2MLH, Mumbai, India) at 50 rpm and temperature was maintained at 37 $\pm$ 0.2 °C. Aliquots samples (1 mL) were collected at predetermined intervals up to 8 h and the amount of drug permeated through the buccal mucosa was then determined at 250 nm using UV spectrophotometer. The experiment was repeated in triplicate ( $n=3$ ) and mean values were calculated. The cumulative amount of the permeated drug was plotted against time. The flux (J) and the permeability coefficient (P) were calculated by using the following equations (1) and (2).

$$J = dQ/dt \quad (1)$$

$$P = (dQ/dt) \Delta CA \quad (2)$$

Where J is flux ( $\text{mg h}^{-1} \text{cm}^{-2}$ ); P is permeability coefficient ( $\text{cm h}^{-1}$ );  $dQ/dt$  is the slope obtained from the steady-state portion of the curve;  $\Delta C$  is the concentration difference across the mucosa and A is the area of diffusion ( $\text{cm}^2$ ).

#### Buccoadhesive tablet preparation

Buccoadhesive tablets were prepared as shown in Table I by direct compression method. Prior to direct compression, QF mixed manually with polymers and perlitol S. D. 200 as a filler and was screened through sieve No. 40 and then lubricants (talc and magnesium stearate) were added. Blending for core and backing layer was carried out separately. First, the backing layer was compressed using 8.0 mm flat faced punches on Cadmach rotary tablet machine (Cadmach, Ahmedabad, India). Then powder of core layer was added to previously obtain backing layer and compressed again (Shanker *et al.*, 2009).

#### Thickness

The thickness of tablets was determined using digital caliper (Aerospace, India). Ten individual tablets were measured and the average thickness was calculated.

#### Weight variation

Weight variation test was carried out for ten tablets of each batch using an electronic balance (Shimadzu, Aux\*200, Japan) and average values were calculated.

#### Hardness

Hardness for three tablets of each batch was mea-

sured by using Monsanto hardness tester and average values were calculated.

#### Assay

Ten tablets were selected randomly and were powdered in a mortar with pestle; powder equivalent to the mass of one tablet was dissolved in methanol by sonication for 30min and filtered through 0.2  $\mu\text{m}$  whattman filter paper. The drug content was analyzed at 250 nm using a UV-Visible spectrophotometer. The experiment was carried out in triplicate and mean drug content was calculated.

#### In vitro bioadhesion studies

Bioadhesion strength of the tablets was determined on a modified physical balance (Shanker *et al.*, 2009; Gupta, Garg, Khar, 1993). This apparatus consists of a modified double beam physical balance in which right pan was replaced with a lighter pan and the left pan was replaced with a glass slide (4 cm length and 2.5 cm width) which was suspended by means of Teflon rings and copper wire. The setup was balanced in such a way that it consists of 5 g of removable weights on right pan and equivalent amount of clay on other side. The height of the total setup was adjusted so as to accommodate a glass container of 6.6 cm height. To find bioadhesion strength, buccal tablet was stack to the glass slide with cyanoacrylate adhesive and balance was set in to weighing mode with the help of a knob that is situated at the base of the balance. Now, 5 g of weight on the right pan is removed. This lowered the glass slide along with the tablet over the membrane with a weight of 5.0 g. The entire setup was kept undisturbed for 5 min. Then, the weights on the right-hand side were slowly added in increments of 0.1 g until the tablet just

**TABLE I** - Composition of quetiapine fumarate (QF) buccal tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
API (mg)	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00
HPMC K4M (mg)	50.00	37.50	25.00	18.75	-	-	-	-	-	-
HPMC K15M (mg)	-	-	-	-	25.00	18.75	12.50	-	-	-
NaCMC (mg)	-	-	-	-	-	-	-	-	-	-
Carbopol (mg)	-	-	-	-	-	-	-	10.00	10.00	5.00
HPC (mg)	-	-	-	-	-	-	-	40.00	15.00	20.00
Perlitol (mg)	42.00	54.50	67.00	73.25	67.00	73.25	79.50	42.00	67.00	67.00
Magnesium stearate (mg)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Talc (mg)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Aspartame (mg)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ethyl Cellulose(mg)	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00

\*All the above formulations contains 1 mg of Magnesium stearate, Talc and Aspartame and Total tablet weight is 150 mg.

\*API-Active pharmaceutical ingredient, HPMCK4M-Hydroxy Propyl Methyl Cellulose K4M, NaCMC-Sodium Carboxy Methyl Cellulose, HPC-Hydroxy Propyl Cellulose, Perlitol as filler.

separated from the membrane surface. The excess weight on the right pan, i.e., total weight minus 5 g, was taken as a measure of the bioadhesive strength.

#### *Ex vivo residence time*

The *ex vivo* residence time of buccal tablets was determined using locally modified USP disintegration apparatus (Nakamura *et al.*, 1996). The disintegration medium was 800 mL phosphate buffer, pH 6.6 maintained at  $37 \pm 0.2$  °C. The buccal membrane of porcine was tied to the surface of a glass slide vertically attached to the apparatus. One surface of tablet was hydrated using 0.5 mL of phosphate buffer, pH 6.6 and then the hydrated surface was brought in contact with the mucosal membrane. The glass slide was vertically fixed to the apparatus and allowed to run in such way that the tablet completely immersed in the buffer solution at the lowest point and was out at the highest point. The time taken for complete erosion or displacement of the tablet from the mucosal surface was noted. The experiments were performed in triplicate (n=3) and mean of triplicate was determined (Tanaka *et al.*, 1980).

#### *Surface pH study*

The bioadhesive tablet was allowed to swell by keeping it in contact with 1 mL of distilled water for 2 h 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 (Bottenberg *et al.*, 1991).

#### *Moisture absorption*

Agar (5%, m/V) was dissolved in hot water and transferred into Petri dishes and allowed to solidify. Six buccal tablets from each formulation were placed in a vacuum oven overnight prior to the study to remove moisture, if any, and laminated on one side with a water impermeable backing membrane. They were then placed on the surface of the agar and incubated at 37 °C for one hour. Then the tablets were removed and weighed and the percentage of moisture absorption was calculated (Agarwal, Mishra, 1999).

#### *In vitro drug release studies*

*In vitro* drug release studies were carried out by using USP XXIII rotating paddle method. The dissolution medium was 500 mL of phosphate buffer pH 6.6 with 0.5% SLS at 50 rpm maintained at  $37 \pm 0.2$  °C. The backing layer of tablet was attached to the glass slide with cyanoacrylate adhesive and then it was placed in dissolution vessel. Aliquot samples (5 mL) were withdrawn at predetermined time intervals and equivalent amount was replaced with

fresh pre-warmed medium. The samples were filtered through whatman filter paper and analyzed at 250 nm using a UV-Visible spectrophotometer.

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

*Ex vivo* permeation of QF from buccoadhesive matrix tablet through the porcine buccal membrane was studied by Franz diffusion cell. The membrane was mounted between donor compartment and receptor compartment. After the buccal membrane was equilibrated for 30 min with phosphate buffer, pH 6.6 between both the compartments, receptor compartment was filled with fresh buffer solution, pH 6.6. The buccal tablet was placed in the donor chamber in such a way that core tablet attaches to the buccal membrane (Vamshi Vishnu, 2007.). Aliquot samples (1 mL) were withdrawn at predetermined time intervals and equivalent amount was replaced with fresh prewarmed medium. The samples were filtered through whatman filter paper and analyzed at 250 nm using a UV-Visible spectrophotometer.

#### *In vivo mucoadhesive performance of buccal tablets*

*In vivo* studies were performed by applying tablets to gums of five healthy volunteers (aged 22-26 years) to obtain the subjective parameters, the residence time and loss of the fragment and the possible production of irritation or pain. Optimized placebo (F3) tablet was given to volunteers and was asked to record the time of application and time of displacement of tablet and to collect information regarding parameters such as irritancy, comfort, taste, dry mouth, salivation and heaviness of the system at the place of application. Food intake was avoided from 0.5 h before beginning of the study to the end of the study but water intake is permitted after the initial 0.5 h (Periolia *et al.*, 2004).

#### *FTIR studies*

The buccoadhesive tablets (F3) were compressed and powdered. The palletized powder, along with KBr, was used for FTIR studies. The IR spectra were recorded using an IR-spectrophotometer (Perkin Elmer FT-IR, Perkin Elmer, USA) for drug (QF), HPMC K4M and optimized formulation.

## RESULTS AND DISCUSSIONS

### **Solubility studies**

Solubility of QF in the phosphate buffer, pH 6.6 was conducted and it was found to be 3.4 mg/mL. The study was conducted in phosphate buffer, pH 6.6 (Shanker

**TABLE II** - Physico-chemical parameters of quetiapine fumarate buccal tablet

Formulation code	Thickness (mm)	Weight Variation (mg)	Friability (%)	Hardness (kg/cm <sup>2</sup> )	%Drug content
F1	2.69±0.020	150.0±0.35	0.08	6.4±0.12	99.66
F2	2.63±0.060	148.1±0.70	0.42	5.2±0.24	101.10
F3	2.51±0.024	152.8±0.25	0.06	7.7±0.10	100.62
F4	2.69±0.015	149.2±0.55	0.28	5.1±10.12	99.63
F5	2.36±0.020	146.0±0.24	0.17	4.8±0.33	101.17
F6	2.64±0.010	155.2±0.70	0.07	6.6±0.10	99.04
F7	2.71±0.030	156.3±0.20	0.31	5.1±0.05	100.39
F8	2.63±0.060	148.1±0.70	0.42	5.2±0.24	101.10
F9	2.61±0.030	157.2±0.50	0.23	4.5±0.05	99.03
F10	2.50±0.035	153.5±0.15	0.04	6.1±0.05	100.43

*et al.*, 2009.). The flux and permeability coefficient of drug solution was found to be 0.3855 mg h<sup>-1</sup> cm<sup>-2</sup> and 0.01542 cm h<sup>-1</sup>, respectively.

#### Thickness, weight variation, hardness, friability and assay

The thickness, weight variation, hardness and assay of the buccal tablets (Table II) were found to be within the prescribed limits. Hardness of the tablets was ranging from 4.5 kg cm<sup>-2</sup> to 7.7 kg cm<sup>-2</sup> as the compression force adjusted to meet the requirements of buccal bilayered tablets. Thickness of the tablets varied from 2.36 mm to 2.71 mm and compared with the theoretical value (2.7 mm). The assay values were also within the limits 99.04%-101.17% due to the proper blending of the drug and excipients. Friability of the tablets varied from 0.04 to 0.42% probably due to the good binding and compressibility of the selected excipients and drug.

#### In vitro bioadhesion studies

The bioadhesion strength, *ex vivo* residence time and surface pH of all formulation were given in Table III. Longer and Robinson (Longer, Robinson, 1986) defined the term bioadhesion as the attachment of a synthetic or natural macromolecule to mucus and/or an epithelial surface. Mucoadhesion takes place in four major stages: wetting, interpenetration, adsorption and formation of secondary chemical bonds between mucus membrane and polymer. The factors like molecular weight of the polymer, contact time with membrane, degree of swelling of the polymer and the type of biological membranes used in the study affect the strength of mucoadhesion (Park, Robinson, 1987). The maximum (41.1 mj) and minimum bioadhesion

strength (17.2 mj) was found in the formulation F8 and F4, respectively. The bioadhesion strength increased as the polymer concentration increased (Vamshi Vishnu *et al.*, 2007). The order of bioadhesion was HPMC K4M > HPMC K15M > Carbopol. Formulations containing HPMC K15M and carbopol showed stronger bioadhesion strength than formulation containing HPMC K4M. Very strong bioadhesion could damage the epithelia of the buccal mucosa (Vamshi Vishnu *et al.*, 2007). Carbopol 934 is reported to be responsible for the formation of the hydrogen bonds between the mucus and functional groups of the polymer. HPC was used to provide adhesion and controlled drug release.

#### Ex vivo residence time

The bioadhesion strength, *ex vivo* residence time and surface pH of all formulation were given in Table III. The minimum and maximum *ex vivo* residence time were found to be 4.05 h and 7.70 h, respectively. The optimized formulation (F3) showed *ex vivo* residence time of 5.15h. As the polymer concentration increased, bioadhesion strength and *ex vivo* residence time increased (Vamshi Vishnu *et al.*, 2007).

#### Surface pH study

The bio-adhesion strength, *ex vivo* residence time and surface pH of all formulation were given in Table III. In order to know the irritation potential *in vivo*, surface pH study was performed because acidic or alkaline pH may cause irritation to the mucosa. Surface pH of the optimized formulation F3 was found to be 7.18 (near to alkaline pH) suggesting that it do not cause any irritation to the mucosa.

#### Moisture absorption

The moisture absorption studies of tablets give an

**TABLE III** - The bioadhesive strength, residence time, surface pH and moisture absorbed values of quetiapine fumarate tablets

Formulation code	Bio adhesion Strength (gm)	<i>Ex vivo</i> residence time(hr)	Surface pH	Moisture absorbed (%)
F1	27.0±0.24	6.14±0.23	7.05±0.070	29.6±1.2
F2	20.6±0.34	5.70±0.16	5.91±0.010	30.3±3.5
F3	19.8±0.04	5.15±0.20	7.18±0.085	32.2±1.4
F4	17.2±0.19	4.05±0.25	6.21±0.015	43.±2.7
F5	29.3±0.06	6.74±0.14	6.81±0.035	31.5±1.6
F6	25.5±0.07	6.26±0.31	6.85±0.015	36.9±0.9
F7	21.0±0.21	5.15±0.35	6.13±0.010	47.8±1.9
F8	41.1±0.27	7.70±0.15	6.92±0.015	52.3±2.6
F9	40.8±0.07	7.03±0.25	6.85±0.030	68.1±1.5
F10	37.0±0.18	6.25±0.35	6.63±0.050	71.7±2.9

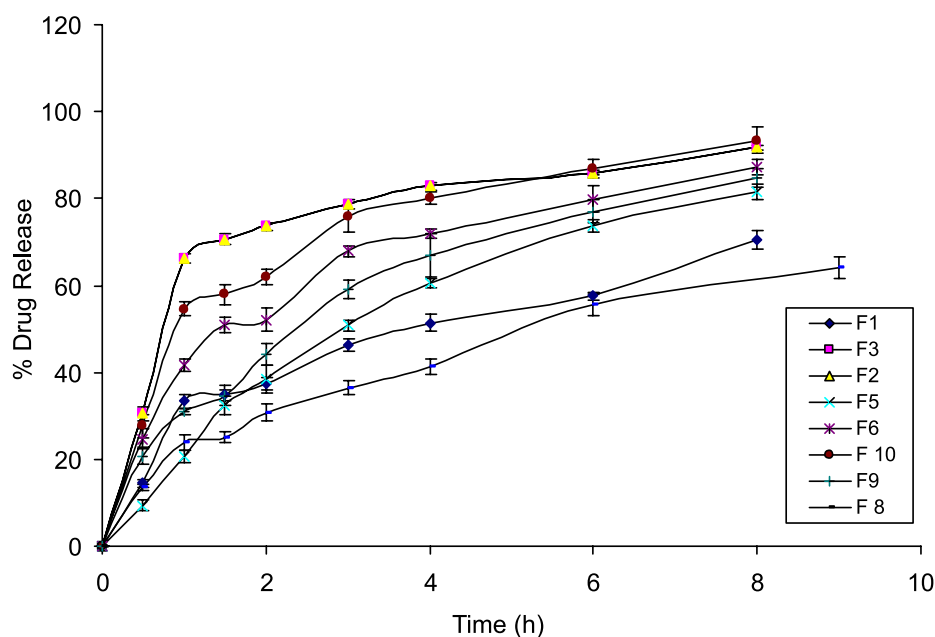
indication of the relative moisture absorption capacities of polymers and whether the formulations would maintain their integrity after moisture absorption. The order of increasing moisture absorption was HPMC K4M < HPMC K15M < Carbopol 934 (Table III). The higher moisture absorption of Carbopol 934 may be due its predominant hydrophilic nature.

#### *In vitro drug release studies*

The *in vitro* drug release profiles of all formulations were shown in Figure 1. The drug release from buccoadhesive tablets observed to be varied according to the type and ratio of matrix forming polymers. Formulations

F3 and F7 showed burst release which was due to lower concentration of HPMC K4M and HPMC K15M. An increase in polymer concentration resulted in an increase in the viscosity of the gel and creates thick gel barrier with longer diffusional path length leading to decrease in diffusion coefficient of the drug and hence a reduction in cumulative percentage of drug release (F5 and F6). Tablets containing lower concentration of either HPMC K4M, HPMC K15M or carbopol 934P respectively have shown a tendency to release the drug in shorter time periods, while the release slowed down as the concentration of the polymer increased.

Formulation F3 ( $91.7 \pm 0.51\%$ ) composed of 1:1

**FIGURE 1** - Mathematical model fitting of *in vitro* drug release.

**TABLE IV** - Release kinetics and mechanism of optimized formulation

Formulation code	Mathematical models(Kinetics)				
	Zero order	First order	Higuchi	Peppas model	
F3	R <sup>2</sup>	R <sup>2</sup>	R <sup>2</sup>	n	R <sup>2</sup>
	0.9988	0.9950	0.9913	0.398	0.9965

drug: HPMC K4M ratio; F6 ( $87.1 \pm 1.84\%$ ) 1:0.75 drug: HPMC K15M ratio and F10 ( $93.4 \pm 3.06\%$ ) containing carbopol 934P (5mg) and HPC (20mg) showed maximum release among their respective series. Optimized formulation (F3) was containing the less quantity (25 mg) of HPMC K4M, and achieved the required bio adhesive and other properties required for buccal tablets compared to rest of the formulations. Hence, it was selected as optimized formulation. F4 and F7 formulations containing 1:0.75 drug: HPMC K4M and 1:0.5 drug: HPMC K15M disintegrated within 4 hrs because of low concentration of polymer. Increasing the concentration of the polymer in the formulations showed a sustained effect on QF release. The rapidly hydrating polymer dominated in controlling the release of QF from the buccal tablets, as seen from the dissolution profiles and moisture absorption data. Release rates slowed down when the concentration of HPMC K4M or HPMC K15M or Carbopol 934P increased from 1:1 to 1:2 ratios and 1:0.5 to 1:1 in F1-4, F8-10 and F5-7, respectively. This is because as the proportion of these polymers in the matrix increased, there was an increase in the amount of water uptake and proportionally greater swelling leading to a thicker gel layer.

#### Mathematical model fitting of *in vitro* drug release

The *in vitro* percentage drug release of optimized formulation F3 was attempted to fit into mathematical models. The n and R<sup>2</sup> values for zero-order, first-order and Higuchi and Peppas (Costa, Sousa Lobo, 2001) were represented in Table IV. The Peppas model is widely used, when the release mechanism is not well known and when more than one type of release is involved (Peppas, 1985). The semiempirical equation is shown as Eq. 3:

$$M_t/M_\infty = kt^n \quad (3)$$

Where  $M_t/M_\infty$  is fraction of the drug released at time t; k represents a constant, incorporating structural and geometrical characteristics of the buccal devices; and n is the diffusion exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0, while in case of Fickian diffusion,  $n=0.5$ ; for zero

order release (case II transport),  $n=1$ ; and for supercase II transport, n is greater than 1. Observation of all the R<sup>2</sup> values indicated that the highest R<sup>2</sup> (0.9988) value was found for Zero order release. According to 'n' value it is less than 0.5, so it follows Fickian diffusion with zero order release.

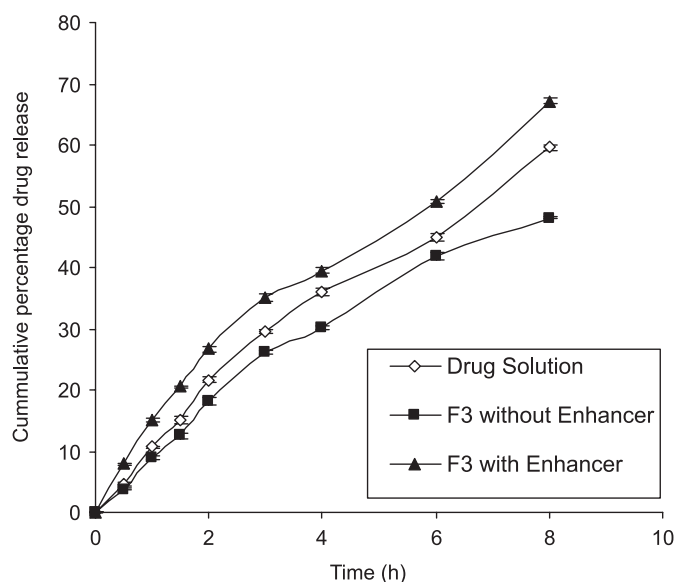
#### Ex vivo permeation of buccal tablets

Based on *in vitro* drug release studies and the results obtained therein and bioadhesion strength of all formulations, formulation F3 was selected for *ex vivo* permeation study. Porcine buccal mucosa resembles that of the human in terms of structure and composition. Hence, porcine buccal mucosa was selected for study. The flux, permeability coefficient and cumulative drug permeated from formulation F3 with enhancer were found to be  $0.398 \text{ mg h}^{-1} \text{ cm}^{-2}$ ,  $0.015528 \text{ cm/h}$  and  $67.2 \pm 0.4\%$  respectively. The flux, permeability coefficient for drug solution and formulation F3 with sodium deoxycholate enhancer and without enhancer were shown in Table V. Presence of enhancer (sodium deoxycholate) increases the diffusivity of the drug via transcellular and paracellular routes. This is due to extraction of lipids from the cell membrane along with the extraction of mucosal lipid from the intercellular spaces by the formation of micelles (Hoogstraate *et al.*, 1997.) and causing uncoiling and extension of the protein helices leading to opening of the polar pathways for diffusion. All these effects increase the permeation of the drug. Cumulative percentage drug permeated of F3 formulation was shown in Figure 2.

**TABLE V** - Flux and Permeability coefficient values of drug solution and formulation

Formulation code	Flux ( $\text{mg h}^{-1} \text{ cm}^{-2}$ )	permeability coefficient (cm/h)
Drug solution	0.385	0.01542
F3 without enhancer	0.326	0.01305
F3 with enhancer	0.398	0.015528

Porcine buccal mucosa resembles that of the human in terms of structure and composition. Hence,



**FIGURE 2** – *In vitro* Drug Release of Optimized formulation with Enhancer, Without Enhancer and Drug Solution.

porcine buccal mucosa was selected for the study. The flux, permeability coefficient and cumulative drug permeated from formulation F3 with enhancer were found to  $0.398 \text{ mg h}^{-1} \text{ cm}^{-2}$ ,  $0.015528 \text{ cm/h}$  and  $67.2 \pm 0.4\%$ , respectively. The flux, permeability coefficient for drug solution and formulation F3 with enhancer and without enhancer were shown in Table V. Presence of enhancer (sodium deoxycholate) increases the diffusivity of the drug via transcellular and paracellular routes. This is due to the extraction of lipids from the cell membrane along with the extraction of mucosal lipids as a result of formation of micelles (Hoogstraate *et al.*, 1997.) and causing uncoiling and extension of the protein helices leading to opening of the polar pathways for diffusion. All these effects collectively contributed in enhancing the permeation of the drug. Cumulative percentage of drug permeated of F3 formulation was shown in Figure 2.

#### *In vivo mucoadhesive performance of buccal tablets*

The results of volunteers to each subjective parameter was shown in Table VI. From the study, it was observed that slight bitter taste was perceived at 4h due to higher swelling of polymer which is responsible for increased thickness of the buccal tablet and this led to improved radial release of QF. This radial release might be responsible for slight bitter taste.

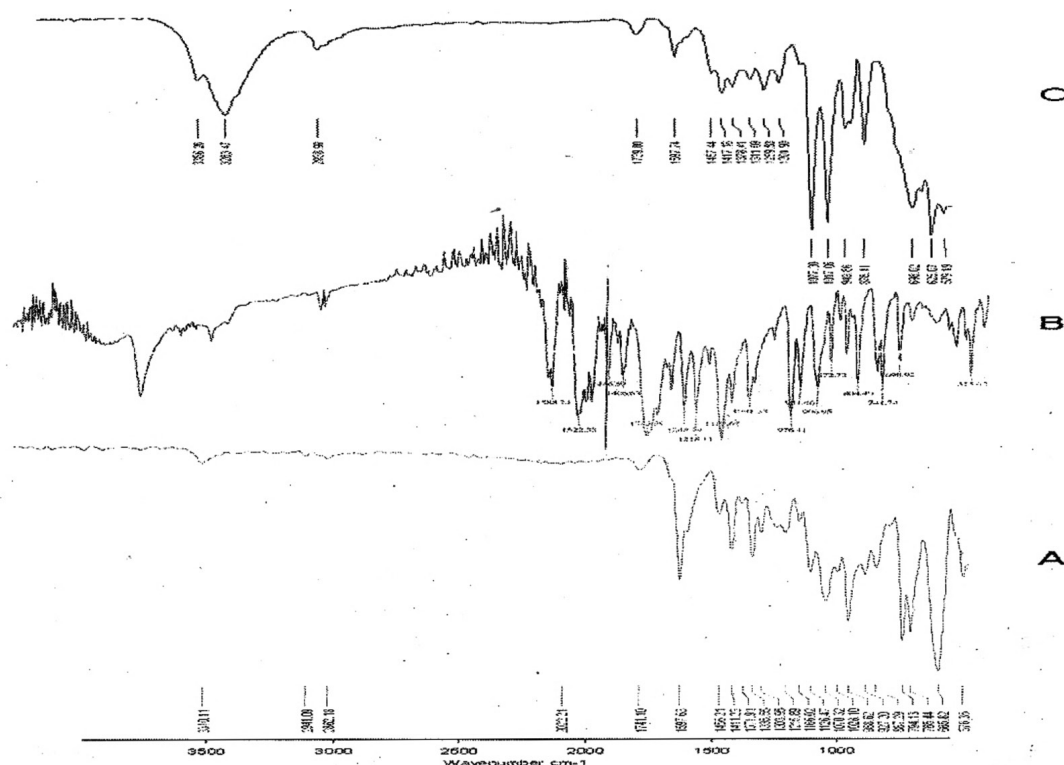
#### **FTIR studies**

FTIR spectra of Quetiapine Fumarate (Figure 3 A) showed peaks of 3310, 2941, 1741, 1597, 1371 and

**TABLE VI** - Response of Healthy Human Male Volunteers to Various Subjective Parameters (n=3)

S. NO.	Criteria	Volunteer's response (%)
1	Irritation	
	None	100
	Slight	-
	Moderate	-
	Severe	-
2	Taste	
	Normal	85
	Slightly	15
	Very unpleasant	-
	Pleasant	-
3	Comfort	
	Very comfortable	-
	Comfortable	90
	Slightly uncomfortable	10
	Moderately uncomfortable	-
4	Dryness of mouth	
	None	85
	Slight	15
	Moderate	-
	Severe	-
5	Salivary secretion	
	None	30
	Slight	50
	Moderate	20
	Severe	-
6	Heaviness at the place of attachment	
	None	95
	Slight	5
	Moderate	-
	Severe	-
7	Dislodgement of the system during study	
	No	100
	Yes	-





**FIGURE 3** - FTIR spectra of A) Drug (quetiapine fumarate), B) Polymer (HPMC K4M), C) Optimized formulation.

1070  $\text{cm}^{-1}$  due to  $-\text{OH}$  stretching, C-H stretching, C=O stretching, N-H bending, C-H bend in plane and C-C stretching respectively.

FTIR Spectra of HPMC K4M (Figure 3 B) showed peaks of 3283, 1446, 1407, 1248, 951 and 872  $\text{cm}^{-1}$  due to C-H stretching, O-H stretching and C-C stretching respectively.

FTIR spectra of optimized formulation (Figure 3 C) showed both characteristics peaks of drug and polymer indicating no drug-polymer interaction.

## CONCLUSION

The present work was aimed at developing a buccoadhesive Quetiapine Fumarate tablets. Progressive hydration technology was employed by using various grades of HPMC in combination with carbopol and HPC for their reported buccoadhesive and release rate controlling abilities. Directly compressed optimized formulation F3 containing HPMC K4M in a drug: polymer ratio (1:1) showed good bioadhesive strength, 91.5% *in vitro* drug release in 8 hours and 85% permeation through porcine buccal mucosa. These findings suggested that buccoadhesive tablets of Quetiapine Fumarate tablets could be prepared by employing direct compression method and

improvement in drug permeation through buccal mucosa contributing to significant improvement in oral bio availability of the drug.

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