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DESIGN AND IN-VITRO CHARACTERIZATION OF FROVATRIPTAN TABLETS FOR BUCCAL DRUG DELIVERY SYSTEM

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ABSTRACT

Frovatriptan is a triptan drug developed by Vernalis for the treatment of migraine headaches and for short term prevention of menstrual migraine.The product is licensed to Endo Pharmaceuticals in North America and Menarini in Europe. The aim of the present study was to develop buccal formulation of Frovatriptan to maintain constant therapeutic levels of the drug for over 12 hrs. HPMCK4M, HPMCK15M and Locust bean gum were employed as polymers. Frovatriptan dose was fixed as 2.5 mg. Total weight of the tablet was considered as 60 mg. Polymers were used in the concentration of 5 mg, 10 mg and 15 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F3) showed better and desired drug release pattern i.e.,98.03 % in 12 hours. It followed zero order release kinetics mechanism.

Key words: Frovatriptan, Buccal Tablets, HPMCK4M, HPMCK15M and Locust bean gum.

INTRODUCTION

Buccal administration refers to a enteral route of administration by which drugs diffuse through the oral mucosa (tissues which line the mouth) and enter directly into the bloodstream. Buccal administration may provide better bioavailability of some drugs and a more rapid onset of action compared to oral administration because the medication does not pass through the digestive system and thereby avoids first pass metabolism [1].

Overview of the oral mucosa:

Light microscopy reveals several distinct patterns of maturation in the epithelium of the human oral mucosa based on various regions of the oral cavity [2,3]. Three distinctive layers of the oral mucosa are the epithelium, basement membrane, and connective tissues. The oral cavity is lined with the epithelium, below which lies the supporting basement membrane [4].

Drug permeability through buccal mucosa:

There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa: o Transcellular (intracellular, passing through the cell) and; o Paracellular (intercellular, passing around the cell). Permeation across the buccal mucosa has been reported to be mainly by the paracellular route through the intercellular lipids produced by membrane-coating granules [5].

Barriers to penetration across buccal mucosa:

The barriers such as saliva, mucus, membrane coating granules, basement membrane etc., retard the rate and extent of drug absorption through the buccal mucosa. The main penetration barrier exists in the outermost quarter to one third of the epithelium [6].

Membrane Coating Granules or Cored Granules:

In non-keratinized epithelia, the accumulation of lipids and cytokeratins in the keratinocytes is less evident and the change in morphology is far less marked than in keratinized epithelia. The mature cells in the outer portion of non-keratinized epithelia become large and flat retain

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nuclei and other organelles and the cytokeratins do not aggregate to form bundles of filaments as seen in keratinizing epithelia [7].

Basement Membrane:

Although the superficial layers of the oral epithelium represent the primary barrier to the entry of substances from the exterior, it is evident that the basement membrane also plays a role in limiting the passage of materials across the junction between epithelium and connective tissue. A similar mechanism appears to operate in the opposite direction [8]. The charge on the constituents of the basal lamina may limit the rate of penetration of lipophilic compounds that can traverse the superficial epithelial barrier relatively easily.

Mucus:

The epithelial cells of buccal mucosa are surrounded by the intercellular ground substance called mucus with the thickness varies from 40 μm to 300 μm. Though the sublingual glands and minor salivary glands contribute only about 10% of all saliva, together they produce the majority of mucus and are critical in maintaining the mucin layer over the oral mucosa. It serves as an effective delivery vehicle by acting as a lubricant allowing cells to move relative to one another and is believed to play a major role in adhesion of mucoadhesive drug delivery systems [9]. At buccal pH, mucus can form a strongly cohesive gel structure that binds to the epithelial cell surface as a gelatinous layer.

Saliva:

The mucosal surface has a salivary coating estimated to be 70 μm thick, which act as unstirred layer. Within the saliva there is a high molecular weight mucin named MG1 that can bind to the surface of the oral mucosa so as to maintain hydration, provide lubrication, concentrate protective molecules such as secretory immunoglobulins, and limit the attachment of microorganisms [10].

Buccal Dosage Forms:

Type I: It is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing.

Type II: In this type, an impermeable backing layer is superimposed on top of the drug loaded bioadhesive layer, creating a double-layered device and preventing drug loss from the top surface of the dosage form into the oral cavity.

Type III: This is a unidirectional release device, from which drug loss is minimal, since the drug is released only from the side adjacent to the buccal mucosa. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa [11,12].

Buccal Tablets: Tablets have been the most commonly investigated dosage form for buccal drug delivery. Buccal tablets are small, flat, and oval shaped dosage form and unlike conventional tablets allow for drinking and speaking without major discomfort. They soften, adhere to the mucosa and are retained in position until dissolution and/or release is complete. Monolithic and two-layered matrix tablets have been designed for buccal drug delivery. Bioadhesive tablets may be prepared using different methods such as direct compression or wet granulation technique. For buccal drug delivery, the tablets which are inserted into the buccal pouch may dissolve or erode; therefore, they must be formulated and compressed with sufficient pressure only to give a hard tablet [13].

Mechanism of bioadhesion: For bioadhesion to occur, three stages are involved:

1. An intimate contact between a bioadhesive and a membrane either from a good wetting of the bioadhesive and a membrane or from the swelling of bioadhesive.
2. Penetration of the bio-adhesive into the tissue takes place.
3. Inter penetration of the chains of the bioadhesive with mucous takes place. Low chemical bonds can then settle. The bonding between the mucus and the biological substance occurs chiefly through both physical and chemical interactions results from enlargement of the adhesive material and chemical bonds due to electrostatic interaction, hydrophobic interactions, hydrogen bonding and dispersion forces [14].

Theories of Bioadhesion or Mucoadhesion

- Adsorption theory
- Wetting theory
- Diffusion theory Diffusion
- Fracture theory
- Mechanical theory

MATERIALS

Frovatriptan, HPMC K4M, HPMC K15M, Locust bean gum, MCC pH 102, Magnesium stearate, Talc.

METHODOLOGY

Analytical method development:

Determination of absorption maxima:

A solution containing the concentration 10 μg/ ml drug was prepared in pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400

Preparation calibration curve:

100mg of Frovatriptan pure drug was dissolved in 100ml of 6.8 pH phosphate buffer (stock solution)10ml of

solution was taken and make up with100ml of 6.8 pH phosphate buffer(100µg/ml). from this 10ml was taken and make up with 100 ml of 6.8 pH phosphate buffer (10µg/ml). The above solution was subsequently diluted with 6.8 ph phosphate buffer to obtain series of dilutions Containing 2,4,6,8,10 and 12µg/ml of Frovatriptan per ml of solution. The absorbance of the above dilutions was measured at 273 nm by using UV-Spectrophotometer taking 6.8 pH phosphate buffer as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight-line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured.

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit.

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of inter particulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Formulation development of Tablets:

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 7.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Frovatriptan . Total weight of the tablet was considered as 60 mg.

Table 1: Formulation composition for tablets

FormulationNo.	Frovatriptan	HPMCK4M	HPMCK15M	Locust bean gum	Mag.Stearate	Talc	MCC pH 102
F1	2.5	5	-	-	3	3	QS
F2	2.5	10	-	-	3	3	QS
F3	2.5	15	-	-	3	3	QS

F4	2.5	-	5	-	3	3	QS
F5	2.5	-	10	-	3	3	QS
F6	2.5	-	15	-	3	3	QS
F7	2.5	-	-	5	3	3	QS
F8	2.5	-	-	10	3	3	QS
F9	2.5	-	-	15	3	3	QS

**All the quantities were in mg

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined.

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability.

Determination of drug content:

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Frovatriptan were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* drug release studies**

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c $\pm$ 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated 6.8 ph phosphate buffer was removed and pH 6.8 phosphate buffer was added process was continued from upto 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 273 nm using UV-spectrophotometer.

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$$F = K_o t$$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$\text{Log } (100\text{-}F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\ t1/2$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time

according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t/ M_\infty = K t^n$$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional 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 I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

Hixson-Crowell release model:

$$(100-Q_t)^{1/3}= 100^{1/3}– K_{HC}.t$$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets) [15,16].

RESULTS

The present study was aimed to developing buccal tablets of Frovatriptan using various polymers. All the formulations were evaluated for physicochemical properties and invitro drug release studies.

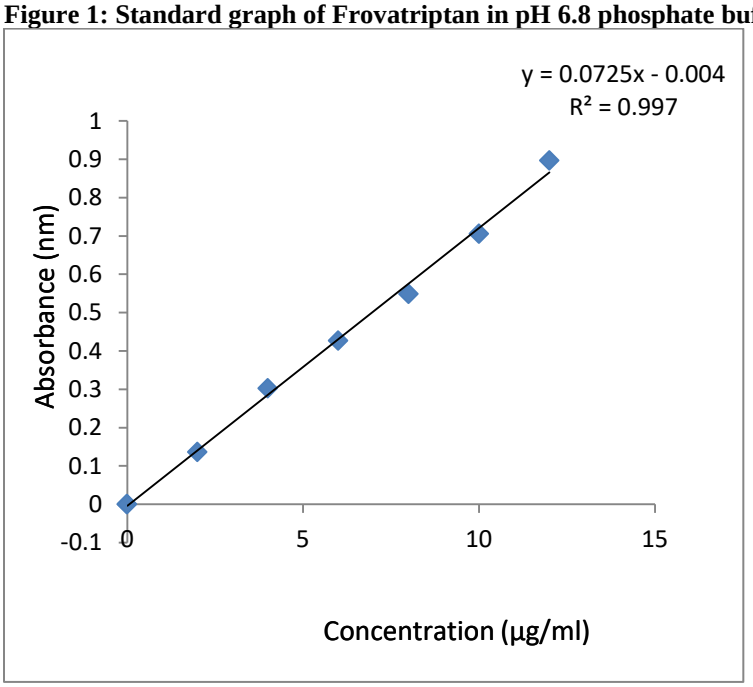
Analytical Method

Graphs of Frovatriptan was taken in buccal pH that is in p H 6.8 phosphate buffer at 273 nm

Table 2: Observations for graph of Frovatriptan in p H 6.8 phosphate buffer (273 nm)

Conc [µg/l]	Abs
0	0
2	0.136
4	0.302
6	0.426
8	0.548
10	0.705
12	0.896

Figure 1: Standard graph of Frovatriptan in pH 6.8 phosphate buffer (273 nm)



Pre-formulation parameters of powder blend

Table3: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	24.08	0.51	0.56	16.18	0.89

F2	23.71	0.54	0.54	16.91	0.98
F3	25.48	0.52	0.60	17.08	0.67
F4	23.39	0.53	0.56	17.73	1.14
F5	25.28	0.54	0.59	16.89	1.05
F6	26.18	0.55	0.58	17.72	1.08
F7	24.21	0.56	0.61	16.38	0.79
F8	23.18	0.58	0.69	17.95	1.17
F9	25.12	0.57	0.54	16.62	1.19

**All the pre-formulation studies were found to be within the limits

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the formulation of tablet.

Table 4: post compression parameters

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	58	4.5	0.57	2.4	98.51
F2	61	4.4	0.54	2.5	96.28
F3	60	4.6	0.53	2.3	99.72
F4	57	4.3	0.56	2.4	97.81
F5	62	4.4	0.51	2.6	98.39
F6	58	4.7	0.53	2.5	96.28
F7	61	4.6	0.55	2.7	97.62
F8	64	4.5	0.53	2.5	96.58
F9	60	4.2	0.54	2.6	98.09

Invitro quality control parameters for tablets

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In-Vitro* Drug Release Studies**

Figure 2: Dissolution profile of Frovatriptan (F1, F2, F3 formulations).

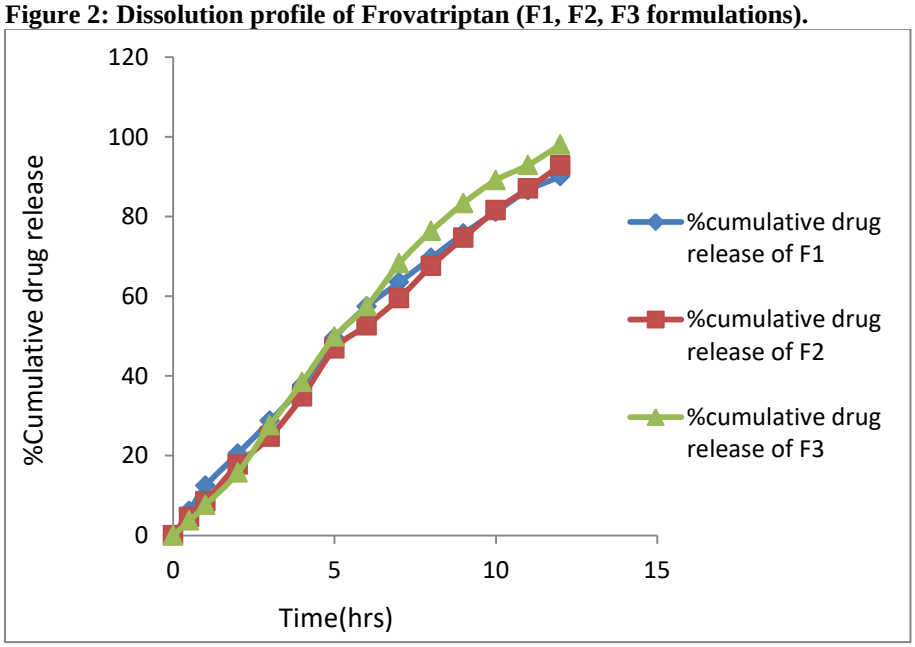


Figure 3: Dissolution profile of Frovatriptan (F4, F5, F6 formulations)

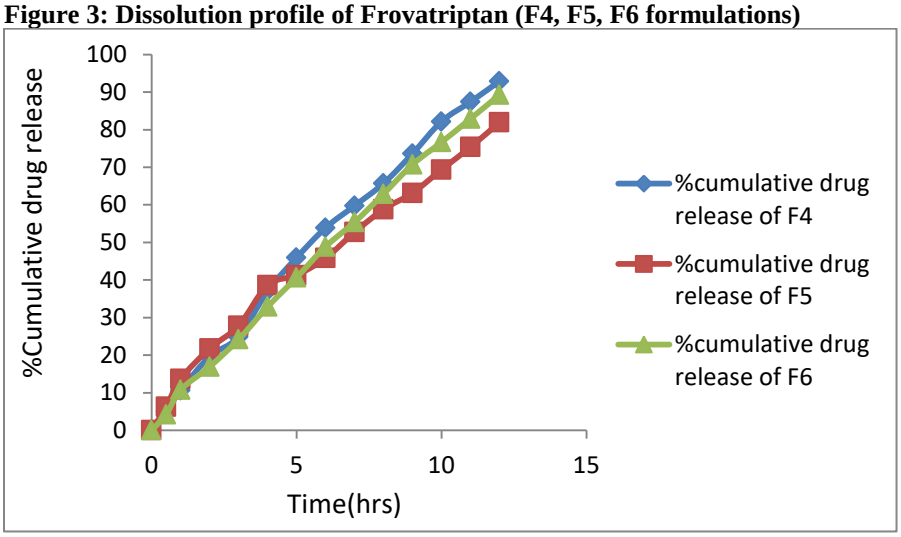


Figure 4: Dissolution profile of Frovatriptan (F7, F8, F9 formulations)

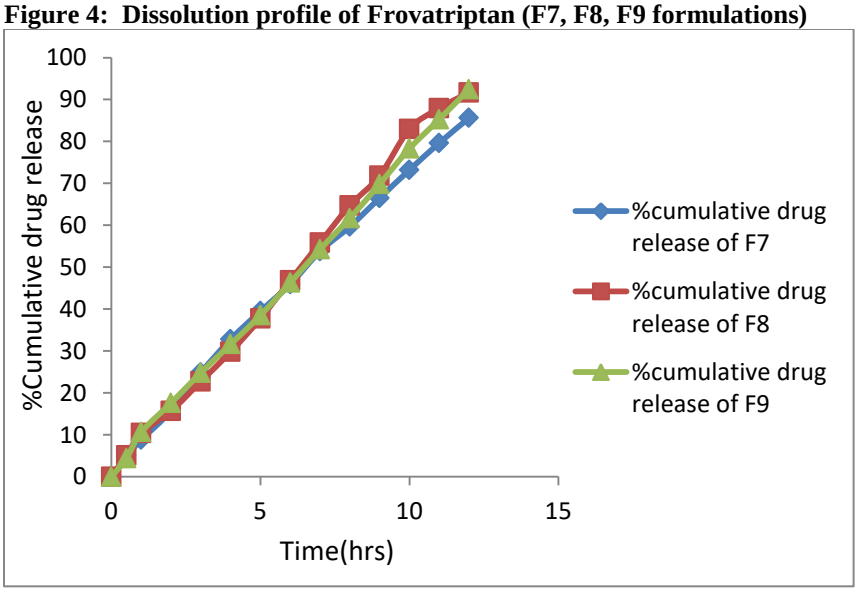


Figure 5: Zero order release kinetics graph

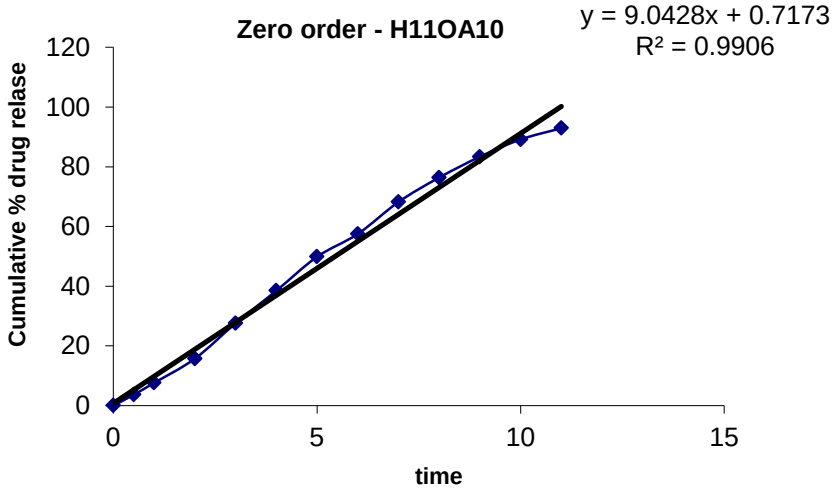


Figure 6: Higuchi release kinetics graph

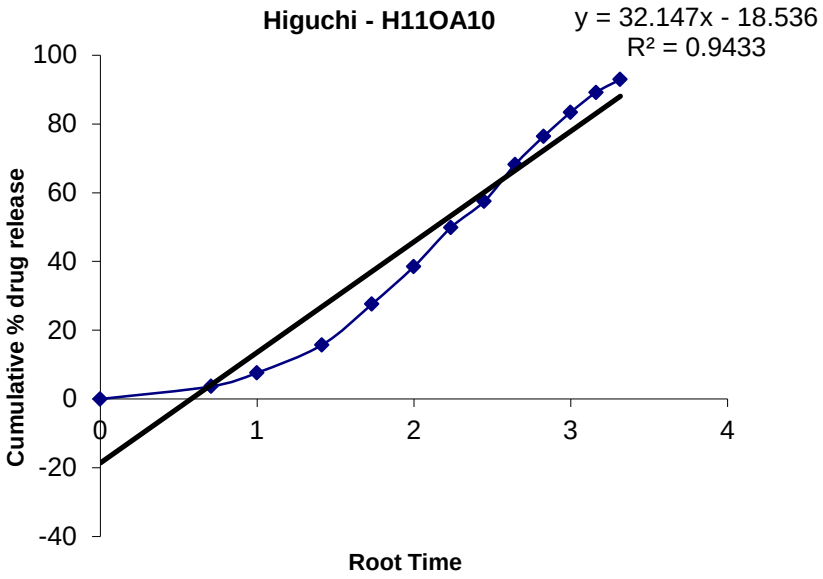


Figure 7: Kars mayerpeppas graph

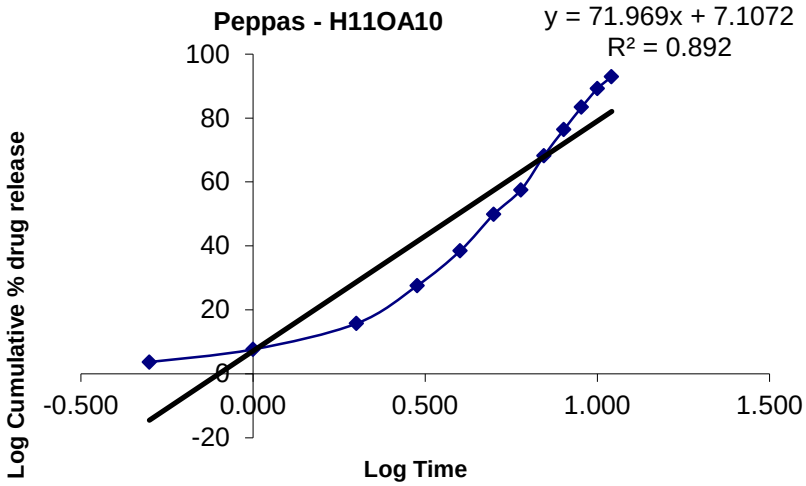
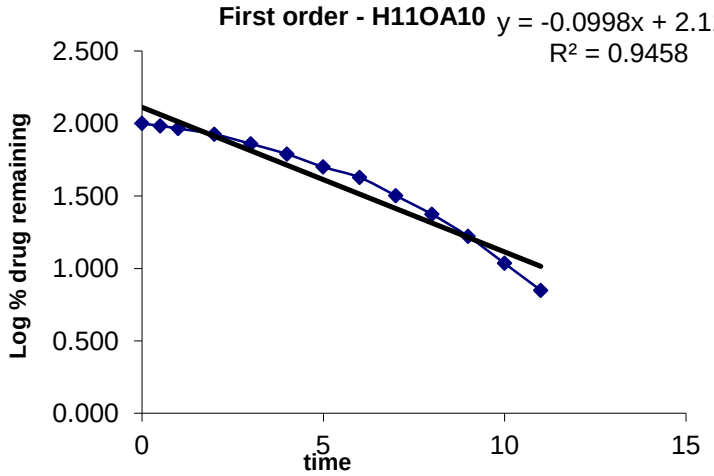


Figure 8: First order release kinetics graph



Drug and Excipient Compatability Studies:
Figure 9: FTIR spectrum of pure drug

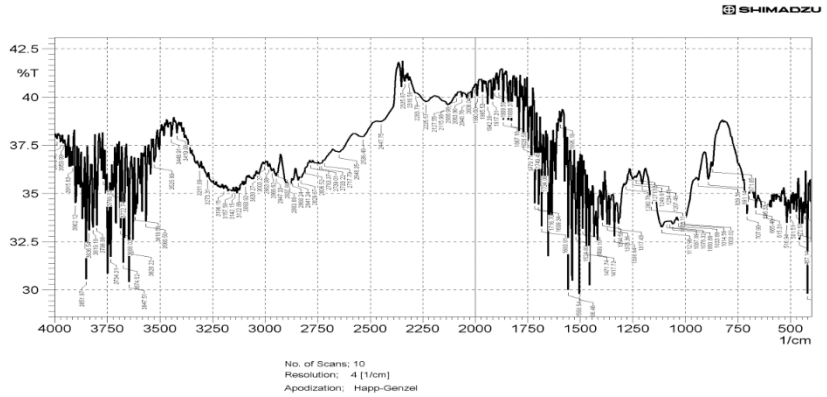
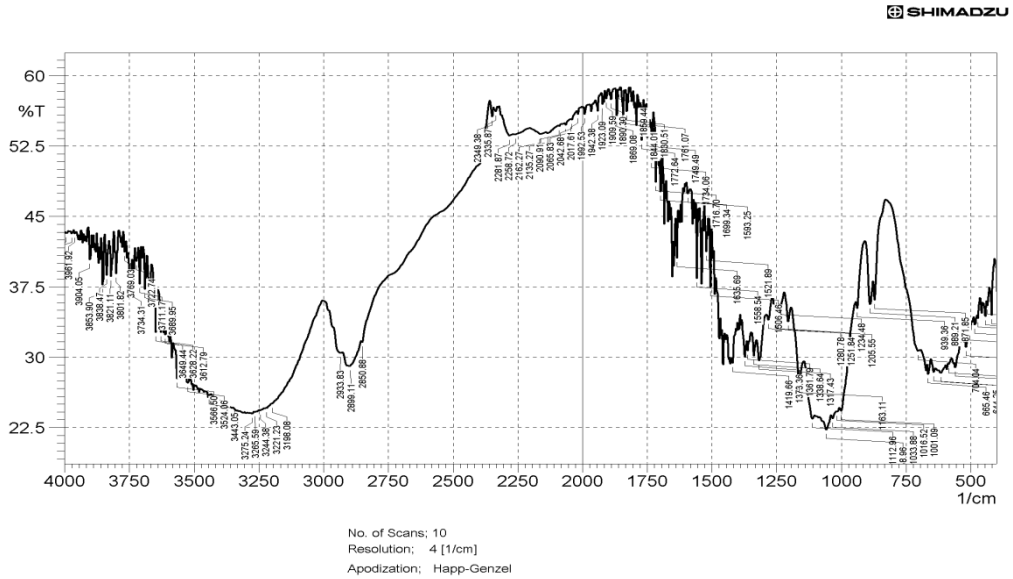


Figure 10: FTIR spectrum of optimised formulation



DISCUSSION

In the design and in-vitro characterization of frovatriptan tablets for buccal drug delivery, the focus was on enhancing drug absorption through the buccal mucosa. The formulated tablets demonstrated promising features, including controlled release and improved drug permeation. The choice of excipients played a crucial role in optimizing drug delivery characteristics. The in-vitro results indicate the potential of these tablets to provide a viable alternative for efficient frovatriptan delivery. Further investigations, including in-vivo studies, will be essential to validate the clinical efficacy and safety of this buccal drug delivery system, offering a novel approach to migraine therapy.

CONCLUSION

The aim of the present study was to develop buccal formulation of Frovatriptan to maintain constant therapeutic levels of the drug for over 12 hrs. HPMCK4M, HPMCK15M and Locust bean gum were employed as polymers. Frovatriptan dose was fixed as 2.5 mg. Total weight of the tablet was considered as 60 mg. Polymers were used in the concentration of 5 mg, 10 mg and 15 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F3) showed better and desired drug release pattern i.e.,98.03 % in 12 hours. It followed zero order release kinetics mechanism

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