

## Preparation, Optimization and *In Vivo* Evaluation of Eletriptan Hbr Fast Dissolving oral Films

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### Abstract

The present investigation was aimed with the objective of developing fast dissolving oral films of Eletriptan HBr in order to attain quick onset of action for the better management of migraine attack. Twenty five formulations were prepared by solvent casting method using different polymer types, plasticizer types, surfactant concentrations and different ratio of hydroxypropyl methyl cellulose and maltodextrin. The prepared films were evaluated for folding endurance, thickness, drug content, in vitro/in vivo disintegration time, drug release and tensile test. The optimized formulation F17 containing HPMC 15cp and maltodextrin showed minimum in vitro disintegration time 11 seconds, highest dissolution rate i.e. 98.5% of drug within 10 min. The optimized film was further evaluated for bioavailability compared with a marketed product (Relpax-20mg). The pharmacokinetic results revealed that the fast dissolving oral films has higher peak blood concentration ( $C_{max}$ ,  $0.455 \pm 0.1 \mu\text{g/ml}$ ) within shorter time ( $T_{max}$ , 0.5 hours), indicating rapid absorption and faster onset of action with acceptable bioavailability value. Therefore, the oral fast dissolving film is considered to be potentially useful for the treatment of migraine disease where quick onset of action is desired, also improved patient compliance.

**Keywords:** Eletriptan HBr, Migraine, Fast dissolving oral films, disintegration time, HPMC, Pharmacokinetics.

### Introduction

Rapidly dissolving or quick dissolving dosage forms have acquired great importance in the pharmaceutical industry due to their unique properties and advantages 1,2. They undergo disintegration in the salivary fluids of the oral cavity within a minute, where they release the active pharmaceutical ingredient. The major amount of the active pharmaceutical ingredient is swallowed orally with the saliva where subsequent absorption takes place in the gastrointestinal tract 3, 4.

The film is an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market, is easy to handle and administer, maintains a simple and convenient packaging, alleviates unpleasant taste, and is straightforward to manufacture. Oral fast dissolving film (FDF) is one such novel approach to increase consumer acceptance by virtue of rapid dissolution, self administration without water or chewing. The need for non-invasive delivery systems continues due to patient's poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management 5.

Orally fast-dissolving film is new drug delivery system for the oral delivery of the drugs. It was developed on the basis of technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates

and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal and intragastric absorption 6.

When put on the tongue, this film disintegrates instantaneously, releasing the drug which dissolves in the saliva. Some drugs are absorbed from the mouth, pharynx, and oesophagus as the saliva passes down into the stomach. In such cases, the bioavailability of the drug is significantly greater than that observed for conventional tablets 7.

Since the drug is directly absorbed into the systemic circulation, degradation in the gastrointestinal (GI) tract and first pass effect can be avoided 8. These dosage forms possess certain specific advantages like no need of water for disintegration, accurate dosing, rapid onset of action, ease of transportability, ease of handling, pleasant taste and improved patient compliance.

Migraine is a common, chronic disorder with episodic attacks 9. It affects 10-20% of the population during the most productive periods of their working lives, women are affected up to four times more often than men 10. Eletriptan hydrobromide is a selective 5-hydroxytryptamine 1B/1D (5-HT1B/1D) receptor agonist, used in the treatment of migraine attacks. The terminal elimination half-life of Eletriptan is approximately 4 hours, and is primarily metabolized by cytochrome P-450 enzyme CYP3A4 after oral administration. Although Eletriptan is well absorbed after oral administration, it undergoes first pass metabolism leading to a mean absolute oral bioavailability of approximately 50% 11.

The available formulation of Eletriptan HBr in market is an immediate release tablet. Conventional Eletriptan HBr tablets are not suitable where quick onset of action is required. To provide the patients with the most convenient mode of administration, there is a need to develop rapidly dissolving dosage form, particularly one that disintegrates and dissolves/ disperses in saliva and can be administered without need of water. Fast dissolving films are useful in patients such as paediatric, geriatric, bedridden, or developmentally disable who may face difficulty in swallowing conventional tablets. So the patients would be benefited from acute treatment by using proposed drug delivery system. Thus, a fast dissolving film is a unique solid oral dosage form and has valuable advantages. The present study is aim to formulate and characterize the fast dissolving oral films of Eletriptan HBr for rapid onset of action in the management of migraine attack and also to improve the bioavailability of the drug.

## Materials and methods

### Materials

Relpax 20mg film coated tablet was purchased from Pfizer Limited, U.K. Eletriptan HBr was received as a gift sample from MSN labs, Hyderabad, India. Hydroxy Propyl Methyl Cellulose (HPMC E3, E6 & E15) was received by Nectar life sciences, Hyderabad, Maltodextrin DE6, Xanthan gum and Aspartame was gifted from Matrix Labs, Hyderabad. Propylene glycol, Vanillin, Citric acid

Amaranth purchased from SD FINE CHEM LTD, Mumbai. Methanol, Acetonitrile and MilliQ water are of HPLC grade from Sigma Aldrich, Mumbai. All other chemicals used were of analytical grade.

### Methods

#### Preparation of Eletriptan Hydrobromide Films

Twenty five fast dissolving oral films of Eletriptan hydromide with 20mg per 4cm<sup>2</sup> films were prepared (F1-F25), using solvent casting method with different types of polymers and composition was shown in table 1, 2 &3. Different grades (HPMC E3, E6 & E15) of film forming polymers of Hypromellose and maltodextrin DE6 were weighed accurately, added to a small amount of water in a small beaker, covered with an aluminum foil and soaked for 24 hours to ensure complete hydration. Xanthan gum was added the next day in small amounts and the solution was stirred on a magnetic stirrer at 75rpm for first half an hour and later 50rpm for 1.5 hours. Then, propylene glycol was added and stirring continued for 30min at 50rpm. Eletriptan hydrobromide, Aspartame, citric acid, vanillin and amaranth were dissolved in sufficient quantity of dimethyl sulfoxide (DMSO) and added to the polymer mixture. This film forming solution was stirred well to obtain a homogenous solution. The resulting solution was poured into a 9 cm petri dish and allowed to dry in hot air oven at 40 °C for 24 hours, the dried batch carefully removed, cut into desired size<sup>12</sup>.

Table 1: Formulation Trials Using HPMC E3

| Code & Ingredients           | F1    | F2    | F3    | F4    | F5    | F6    |
|------------------------------|-------|-------|-------|-------|-------|-------|
| Eletriptan Hydrobromide (mg) | 317.5 | 317.5 | 317.5 | 317.5 | 317.5 | 317.5 |
| HPMC E3(mg)                  | 300   | 325   | 350   | 375   | 400   | 425   |
| Maltodextrin                 | 250   | 225   | 200   | 175   | 150   | 125   |
| Propylene glycol             | 100   | 100   | 10    | 100   | 100   | 100   |
| Xanthan gum (mg)             | 10    | 10    | 8     | 8     | 8     | 10    |
| Aspartame (mg)               | 20    | 20    | 20    | 20    | 20    | 20    |
| Citric acid (mg)             | 10    | 10    | 10    | 10    | 10    | 10    |
| Water (mL)                   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   |
| Vanilla                      | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   |
| Amaranth                     | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   |
| Dimethyl Sulfoxide           | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   |



Table 2: Formulation Trials Using HPMC E6

| Code & Ingredients          | F7    | F8    | F9    | F10   | F11   | F12   | F13   | F14   | F15   |
|-----------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Eletriptan Hydrobromide(mg) | 317.5 | 317.5 | 317.5 | 317.5 | 317.5 | 317.5 | 317.5 | 317.5 | 317.5 |
| HPMC E6(mg)                 | 300   | 325   | 350   | 375   | 400   | 425   | 450   | 450   | 475   |
| Maltodextrin                | 250   | 250   | 225   | 225   | 200   | 175   | 155   | 100   | 100   |
| Propylene glycol            | 120   | 120   | 130   | 140   | 140   | 140   | 140   | 140   | 140   |
| Xanthan gum (mg)            | 10    | 10    | 10    | 8     | 8     | 8     | 8     | 8     | 8     |
| Aspartame (mg)              | 20    | 20    | 20    | 20    | 20    | 20    | 20    | 20    | 20    |
| Citric acid (mg)            | 10    | 10    | 10    | 10    | 10    | 10    | 10    | 10    | 10    |
| Water (ml)                  | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   |
| Vanilla                     | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   |
| Amaranth                    | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   |
| Dimethyl sulfoxide          | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   |

Table 3: Formulation Trials Using HPMC E15

| Code & Ingredients          | F16   | F17   | F18   | F19   | F20   | F21   | F22   | F23   | F24   | F25   |
|-----------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Eletriptan Hydrobromide(mg) | 317.5 | 317.5 | 317.5 | 317.5 | 317.5 | 317.5 | 317.5 | 317.5 | 317.5 | 317.5 |
| HPMC E15 (mg)               | 300   | 350   | 350   | 375   | 375   | 400   | 400   | 425   | 425   | 450   |
| Maltodextrin                | 200   | 200   | 200   | 175   | 175   | 150   | 150   | 150   | 125   | 125   |
| Propylene glycol            | 120   | 140   | 140   | 140   | 140   | 140   | 140   | 140   | 140   | 140   |
| Xanthan gum (mg)            | 10    | 10    | 10    | 10    | 8     | 8     | 8     | 8     | 8     | 8     |
| Aspartame (mg)              | 20    | 20    | 20    | 20    | 20    | 20    | 20    | 20    | 20    | 20    |
| Citric acid (mg)            | 10    | 10    | 10    | 10    | 10    | 10    | 10    | 10    | 10    | 10    |
| Water (ml)                  | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   |
| Vanilla                     | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   |
| Amaranth                    | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   |
| Dimethyl sulfoxide          | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   | Q.S   |

## Evaluation of Eletriptan HBR oral films

### Physical characterization of FDOFs

Physical characterization of FDOFs can be carried out by visual inspection for characteristics such as colour, thickness, brittleness, peeling ability, transparency, surface smoothness, tack property and film forming capacity.

The prepared films were subjected for in vitro evaluation tests like Thickness, Folding Endurance, Surface pH, Morphological properties, %Drug content, Tensile strength, Percent elongation, In vitro Disintegration time, In vitro Dissolution studies and in vivo studies on rabbits.

### Surface pH

The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 30s. The pH was noted

after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was done 13.

### Weight variation and thickness

For evaluation of film weight and thickness films were taken and weighed individually on a digital balance. The film thickness was measured using Digital Vernier caliper (Mitutoyo) at six different places and the average value was calculated 14.

### Folding endurance

The folding endurance is expressed as the number of folds (number of times the film is folded at the same place) required to break the specimen or to develop visible cracks. This also gives an indication of brittleness of the film. A strip of 2.5 cm × 2.5 cm was subjected to folding endurance by folding the patch at the same



place repeatedly several times until a visible crack was observed, and the values were reported 15.

### %Drug content

Three films (4 cm<sup>2</sup> of each) were transferred in to separate graduated flasks containing 100 ml of phosphate buffer pH 6.8 and continuously stirred for 2 hrs. The solutions were filtered, suitably diluted and analyzed at 221 nm and the drug content was calculated 16.

### Percent Elongation

This mechanical property was evaluated using the Instron universal testing instrument (Model F. 4026, Instron Ltd., Japan) with a 5 kg load cell. The percentage increase in the length of a film (L<sub>2</sub>), when it is pulled under standard conditions of stress just before the point of break is known as percent elongation. The initial length of a film is L<sub>1</sub>, the increase in length is (L<sub>2</sub>-L<sub>1</sub>). It is measured in terms of percentage. Percent elongation and tensile strength was carried for only 4 best formulations.

$$\text{Percent elongation} = \frac{(L_2 - L_1)}{L_1 \times \text{Cross sectional area}} \times 100$$

### Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. Film strip of dimension 5 × 2 cm<sup>2</sup> and free from air bubbles or physical imperfections was held between two clamps positioned at a distance of 3 cm apart. A cardboard was attached on the surface of the clamp via a double sided tape to prevent the film from being cut by the grooves of the clamp. During measurement, the strips were pulled at the bottom clamp by adding weights in pan till the film breaks. The force was measured when the films broke. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below 17.

$$\text{Tensile strength} = \frac{\text{Load at Failure}}{\text{Strip thickness} \times \text{Strip Width}}$$

### In vitro disintegration studies

Disintegration test was performed to ensure the disintegration of the film in phosphate buffer pH 6.8. One film from each formulation was introduced into one tube of disintegration apparatus IP. A disc was added into the tube. The assembly was suspended in a beaker containing phosphate buffer pH 6.8 and the apparatus was operated until the film disintegrated 15.

### In vitro dissolution studies

The phosphate buffer pH 6.8 was taken as the dissolution medium to determine the drug release.

The dissolution profile of quick release films of Almotriptan malate was carried out in USP basket type apparatus containing 300 ml of the phosphate buffer pH 6.8. The film was placed in the basket, maintained at 37 ± 0.5 C and the agitation speed was 50 rpm. Aliquots (5 ml) of the dissolution medium were withdrawn at 1, 2, 4, 6, 8 and 10 minutes time intervals and the same amount was replaced with the fresh medium. Samples were analyzed spectrophotometrically at 221 nm and the cumulative percentage of drug release was calculated 18.

### Drug excipient compatibility studies

The drug excipient compatibility studies were carried out by Fourier Transmission Infrared Spectroscopy (FTIR) method and Differential Scanning Colorimetry (DSC) method.

### Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The IR spectrum of the samples was prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at pressure of seven to ten tons.

### Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. The DSC thermograms were recorded for pure drug, HPMC E15, Maltodextrin, Drug and HPMC mixture and optimized formulation. Accurately weighed samples were placed on aluminium plate, sealed with aluminium lids and heated at a constant rate of 5°C /min, over a temperature range of 0 to 250°C.

### Stability studies

The stability study of the optimized fast-dissolving films was carried out under different conditions according to ICH guidelines. The film was packed in the aluminium foil and stored in a stability chamber for stability studies. Accelerated Stability studies were carried out at 40 °C / 75 % RH for the best formulations for 6 months. The patches were characterized for the drug content and other parameters during the stability study period 15.

### Pharmacokinetic study

### Animal Preparation

Twelve New Zealand white rabbits of either sex were (weighing 2-3 kg) selected for this study, all the animals were healthy during the period of the experiment. Animals were maintained at room temperature 25°C, RH 45% and 12 h alternate light and dark cycle with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. The protocol of animal study was approved





by the institutional animal ethics committee (IAEC NO: P35/VCP/IAEC/2015/DBP/AE12/Rabbits).

### *In vivo* Study design

The rabbits were fasted overnight before administration of the formulations (ODF contain Eletriptan Hydrobromide 20 mg) and Innovator (Relpex 20mg). The rabbits were randomly divided into two groups each group contains six animals. The group A rabbits were anaesthetized with intravenous injection of pentobarbital in a dose of 25mg/kg then positioned on table with the lower jaw supported in a horizontal position and the ODF was carefully placed on the rabbit tongue. The innovator was administered orally to group B with equivalent to animal body weight.

Blood samples for pharmacokinetic analysis were obtained at different time intervals 0, 0.25, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00 & 24.00h after doing. Blood samples were collected in heparinised tubes and were centrifuged for 10min at 3,000 rpm at room temperature.

### Preparation of Plasma Samples for HPLC Analysis

Rabbit plasma (0.5 ml) samples were prepared for chromatography by precipitating proteins with 2.5 ml of ice-cold absolute ethanol for each 0.5 ml of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was re suspended with 1 ml of acetonitrile by vortexing for 1 min. After centrifugation (5000 – 6000 rpm for 10 min), the acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature. Samples were reconstituted in 200  $\mu$ l of 70 % of acetonitrile and 30% water was injected for HPLC analysis.

For HPLC C18 column (ODS-UG-5, 250 4.6 mm, 5 $\mu$ ) and the mobile phase consisting of phosphate buffer: Acetonitrile ratio of 60:40 v/v. At a flow rate of 0.9 ml/min with UV detection at 221 nm.

### Pharmacokinetic Analysis

The pharmacokinetic parameters, peak plasma concentrations ( $C_{max}$ ) and time to reach peak concentration ( $t_{max}$ ) were directly obtained from concentration time data. In the present study,  $AUC_{0-t}$  refers to the AUC from 0 to 24 hrs, which was determined by linear trapezoidal rule and  $AUC_{0-\infty}$  refers to the AUC from time at zero hours to infinity.

The  $AUC_{0-\infty}$  was calculated using the formula  $AUC_{0-t} + [C_{last}/K]$  where  $C_{last}$  is the concentration in  $\mu$ g/ml at the last time point and K is the elimination rate constant.

Various pharmacokinetic parameters like area under the curve [AUC], elimination half life ( $t_{1/2}$ ), Volume of distribution ( $V_d$ ), total clearance ( $Cl_T$ ) and mean residence time for each subject using a non compartmental pharmacokinetic programme. The pharmacokinetic parameters were performed by a non compartmental analysis using Win Nonlin 3.3 $\phi$  pharmacokinetic software (Pharsight Mountain View, CA USA). All values are expressed as the mean  $\pm$ SD. Statistical analysis was performed

with Graph Pad InStat software (version 3.00, Graph Pad Software, San Diego, CA, USA) using one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test. Difference with  $p < 0.05$  was considered statistically significant.

## Results and discussion

### Preparation of Eletriptan Hydrobromide films

Fast dissolving oral films of Eletriptan HBr was prepared with the dose of 20mg per 4cm<sup>2</sup> film. A total of 25 formulations were prepared using three different Hypromellose E3, Hypromellose E6 and Hypromellose E15 and other polymers, the resulting films were shown in Figure 1.

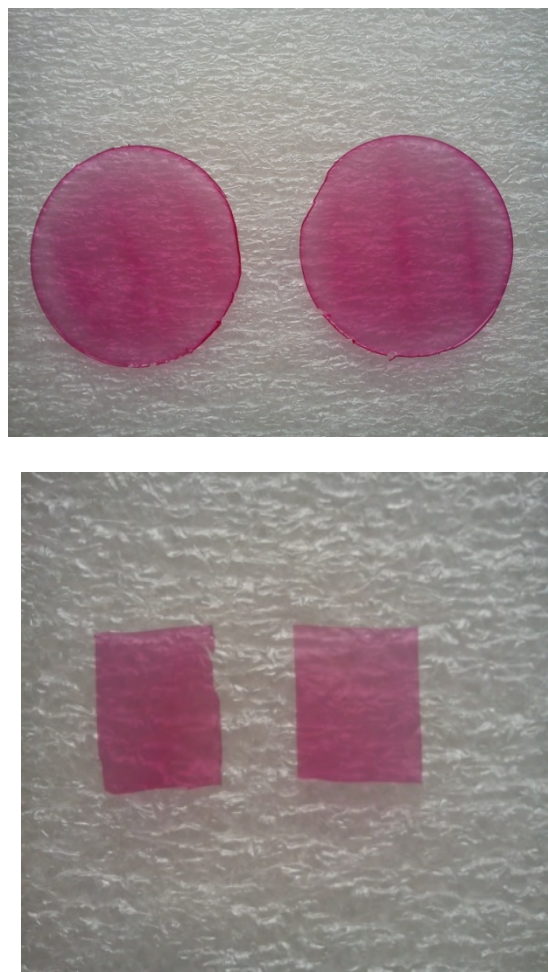


Figure 1: Eletriptan HBr Films



## Physical Characterization of eletriptan HBr films

Physical characterization of FDOFs was carried out by visual inspection and the following results were observed.

The films were evenly colored and no migration of color was observed. The increased thickness of film is attributed to the increase in the amount of HPMC. F1, F2, F4, F5, F6, F9, F10, F11 and F19 were found to brittle in nature due to insufficient amount of plasticizer added to the formulation. F1 to F3 and F6 are difficult to peel whereas others separated easily.

F4, F7, F8, F9, F11, F23 were found to be thick. F15, F22 & F24 were found to be excellent in film forming property, non-tacky, thin, flexible and easy to peel. The films obtained from all the formulations had smooth surface on either side. Formulations

prepared using HPMC E3 was not evaluated for physical parameters and other tests as they fail to satisfy the preliminary characteristics of films due to their poor film forming ability.

## Preliminary Characterization of FDOF'S

Physical characterization of FDOFs was carried out by visual inspection and the following was observed.

The films were evenly coloured and no migration of colour was observed. All the formulations were checked for film property, tack property and brittleness; the results are summarized in Table 4. Formulations F10, F13, F16, F17, F18, F20 and F21 found to have good film forming property, non-tacky, thin, flexible and easy to peel.

**Table 4: Preliminary Characterization of FDOF'S**

| Code and properties | Film property | Tack property | Ease of handling                  |
|---------------------|---------------|---------------|-----------------------------------|
| F1                  | Poor          | Non-tacky     | Brittle, difficult to peel        |
| F2                  | Poor          | Non-tacky     | Brittle, difficult to peel        |
| F3                  | Average       | Tacky         | Slightly thick & brittle          |
| F4                  | Average       | Tacky         | Slightly brittle                  |
| F5                  | Average       | Non-tacky     | Thin, brittle, difficult to peel  |
| F6                  | Average       | Tacky         | Thin, difficult to peel           |
| F7                  | Average       | Tacky         | Thick, difficult to peel          |
| F8                  | Poor          | Non-tacky     | Brittle                           |
| F9                  | Poor          | Non-tacky     | Brittle, slightly Opaque          |
| F10                 | Good          | Non-tacky     | Slightly thick                    |
| F11                 | Good          | Non-tacky     | Slightly thick, opaque            |
| F12                 | Good          | Tacky         | Thin, tough & flexible            |
| F13                 | Good          | Non-Tacky     | Thin, tough& flexible             |
| F14                 | Poor          | Non-tacky     | Brittle                           |
| F15                 | Poor          | Tacky         | Soft, difficult to peel, opaque   |
| F16                 | Good          | Non-tacky     | Easy to peel                      |
| F17                 | Excellent     | Non-tacky     | Thin, flexible and easy to peel   |
| F18                 | Good          | Tacky         | Soft, easy to peel                |
| F19                 | Average       | Non-tacky     | Slightly thick                    |
| F20                 | Good          | Non-tacky     | Soft, Thick, easy to peel         |
| F21                 | Good          | Non-tacky     | Soft, thick& easy to peel         |
| F22                 | Good          | Non-tacky     | Thin, tough& flexible             |
| F23                 | Average       | Non-tacky     | Thick                             |
| F24                 | Poor          | Tacky         | Very thin soft& difficult to peel |

## Evaluation of fast dissolving oral films of Almotriptan malate

### Thickness & Weight variation

Thickness of all mouth dissolving films was measured with Digital Vernier caliper (Mitutoyo). All the mouth dissolving formulations of different polymers are show thickness value in the range of  $73 \pm 1$  to  $91 \pm 1$   $\mu\text{m}$  (Table 5). The optimized film (F17) has thickness of  $87 \pm 2$   $\mu\text{m}$ . When concentration of polymer increases, thickness and

weight of the film also increased. The weight variation of the formulations was in the range of  $50.20 \pm 0.3$  to  $85.5 \pm 0.5$  mg, which was acceptable.

### Folding endurance

Folding endurance gives an indication of brittleness of the film. It was shown that as the concentration of polymer and plasticizer increases, folding Endurance of mouth dissolving film increases. The folding endurance value of the prepared films ranged from



40±1 to 115±3 (Table). The optimized film (F17) has folding endurance value of 105±2, which was desirable.

### Surface pH

Surface pH of all mouth dissolving films prepared by using different polymers was found to be in the range of 6.51 to 6.89 pH (Table) close to the neutral pH, which indicated that films may have less potential to irritate the sublingual mucosa, and hence, more acceptable by the patients. The optimized film (F17) has surface pH value of 6.81.

### %Drug content

All the fast dissolving oral films were found to contain an almost uniform quantity of the drug, as per content uniformity studies

indicating reproducibility of the technique. Drug content in the films was evaluated and the values were found to be between 94.5±0.46 to 98.4±0.5 % (Table) for three different cuts from each film. As per the USP requirements, the films found to meet the criteria for content uniformity. No significant difference in the drug content among the films indicated good content uniformity.

### In vitro disintegration studies

The disintegrating time of all the formulations was ranges from 11±2 to 34±2sec. The results for all the formulations were tabulated in Table 5. The disintegration time of optimized formulation (F17) was found to be 11sec, which was very less and desirable for quick onset of action.

**Table 5: Physical evaluation of fast dissolving oral films of Eletriptan HBr**

| Formulation code | Thickness (µm) | Weight Variation(mg) | Folding Endurance (count) | Surface pH | % Drug content | In Vitro Disintegration time (sec) |
|------------------|----------------|----------------------|---------------------------|------------|----------------|------------------------------------|
| F6               | 73±1           | 50.20±0.3            | 40±1                      | 6.51±0.04  | 94.8±0.24      | 34±2                               |
| F7               | 74±1           | 51.22±0.4            | 53±1                      | 6.62±0.02  | 95.10±0.14     | 30±2                               |
| F8               | 72±1           | 55.5±0.1             | 58±2                      | 6.79±0.03  | 95.45±0.45     | 31±2                               |
| F9               | 79±3           | 54.22±0.1            | 61±1                      | 6.55±0.04  | 94.5±0.7       | 29±2                               |
| F10              | 80±1           | 57.64±0.2            | 53±4                      | 6.70±0.02  | 94.6±0.15      | 29±2                               |
| F11              | 74±1           | 61.3±0.2             | 62±1                      | 6.85±0.1   | 92.54±0.6      | 23±2                               |
| F12              | 88±1           | 63.65±0.3            | 64±2                      | 6.75±0.05  | 96.56±1.2      | 20±2                               |
| F13              | 79±1           | 62.1±0.3             | 59±2                      | 6.68±0.04  | 92.4±0.3       | 18±2                               |
| F14              | 88±0           | 64.2±0.12            | 64±2                      | 6.93±0.01  | 94.3±1.9       | 16±2                               |
| F15              | 89±2           | 85.5±0.5             | 100±2                     | 6.67±0.02  | 95.5±0.8       | 15±2                               |
| F16              | 85±2           | 81.5±0.4             | 90±2                      | 6.56±0.02  | 95.5±0.8       | 14±2                               |
| F17              | 87±2           | 72.5±0.6             | 105±2                     | 6.81±0.01  | 98.4±0.5       | 11±2                               |
| F18              | 91±2           | 62.1±0.2             | 95±2                      | 6.89±0.01  | 96.4±0.5       | 28±2                               |
| F19              | 79±2           | 65.69±0.3            | 115±3                     | 6.67±0.01  | 94.5±0.46      | 26±2                               |
| F20              | 87±0           | 79.2±0.5             | 101±5                     | 6.81±0.02  | 95.7±1.2       | 20±2                               |
| F21              | 87±1s          | 62.3±0.5             | 99±1                      | 6.72±0.05  | 95.2±0.2       | 18±2                               |
| F22              | 87±0           | 65.6±0.4             | 100±2                     | 6.78±0.02  | 94.5±0.01      | 17±2                               |
| F23              | 89±2           | 73.5±0.4             | 104±2                     | 6.74±0.03  | 94.5±0.6       | 14±2                               |
| F24              | 85±2           | 76.2±0.5             | 115±3                     | 6.68±0.01  | 95.56±0.3      | 15±2                               |



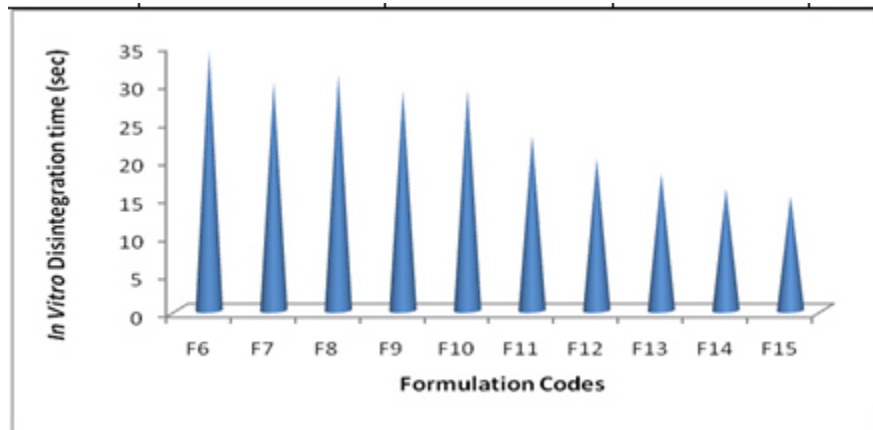


Figure 2: In vitro Disintegration Time of HPMC E6 formulations (F6- F15)

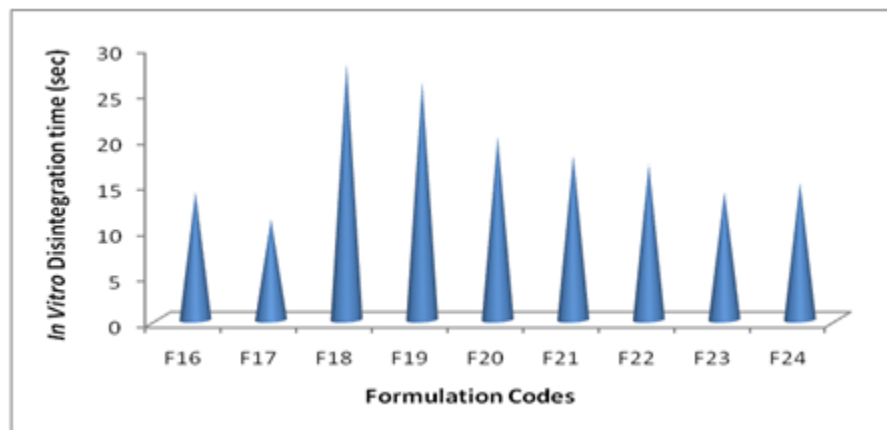


Figure 3: In vitro Disintegration Time of HPMC E15 formulations

### Tensile Strength and Percent Elongation

Tensile strength was performed for selected formulations that are more similar to the optimized formulation.

Table 6: Tensile Strength and Percent Elongation

| Formulation Code | Tensile Strength (g/cm <sup>2</sup> ) | Percent elongation (%) |
|------------------|---------------------------------------|------------------------|
| F16              | 9.2                                   | 8.2                    |
| F17              | 10.6                                  | 9.4                    |
| F23              | 9.7                                   | 8.5                    |
| F24              | 10.4                                  | 9.0                    |

### In vitro Dissolution Studies

### In-vitro drug dissolution study of eletriptan HBr oral dissolving films

The cumulative % drug release for the formulations F7 to F15 and F16 to F24 are tabulated in Table 7 and 8 and Figure 4 and 5 respectively. The optimized formulation (F17) showed highest percent of drug release 98.5 by the end of 10 min when compared with other formulations.

The cumulative % drug release studies of optimized formulation F17 was compared with the marketed RELPAX (20mg) conventional tablet and the drug release of F17 and innovator was found to be 98.5 and 79.4 respectively after 10min, which shown in Table 9 and Figure 6.





Table 7: Cumulative Percentage Drug Release for HPMC E6

| Time (min) | Formulation Code |            |           |           |            |           |           |            |           |  |
|------------|------------------|------------|-----------|-----------|------------|-----------|-----------|------------|-----------|--|
|            | F7               | F8         | F9        | F10       | F11        | F12       | F13       | F14        | F15       |  |
| 0          | 0                | 0          | 0         | 0         | 0          | 0         | 0         | 0          | 0         |  |
| 1          | 35.45±1.4        | 42.04±1.2  | 32.2±3.01 | 38.7±1.12 | 42.5±2.045 | 48.2±2.55 | 44±1.21   | 32.45±1.6  | 29.7±1.4  |  |
| 2          | 50.11±1.11       | 53.48±2.54 | 51.2±1.35 | 45.7±1.58 | 57.3±2.21  | 55.1±3.08 | 52±3.56   | 37.25±1.22 | 55.3±2.55 |  |
| 4          | 55.25±1.23       | 64.82±2.64 | 75.2±2.62 | 64.8±2.09 | 66.5±1.25  | 69.2±2.56 | 73±2.2    | 44.31±2.75 | 68.5±2.72 |  |
| 6          | 68.47±2.65       | 75.65±3.08 | 79±3.55   | 70.2±2.46 | 72.5±1.88  | 74.1±1.59 | 80.8±1.81 | 61.36±2.68 | 70.7±3.05 |  |
| 8          | 84.3±2.02        | 86.6±2.64  | 84.2±2.88 | 74.5±2.55 | 84.6±0.96  | 88.8±1.8  | 85±2.51   | 75.11±2.03 | 80.2±2.65 |  |
| 10         | 88.05±1.85       | 90.8±1.86  | 87.2±1.75 | 82.2±2.71 | 89.9±1.48  | 92±2.81   | 91.92±1.3 | 87.54±1.86 | 84.6±1.89 |  |

Table 8: Cumulative Percentage Drug Release for HPMC E15

| Time | Formulation code |           |            |            |            |            |            |            |            |  |
|------|------------------|-----------|------------|------------|------------|------------|------------|------------|------------|--|
|      | F16              | F17       | F18        | F19        | F20        | F21        | F22        | F23        | F24        |  |
| 0    | 0                | 0         | 0          | 0          | 0          | 0          | 0          | 0          | 0          |  |
| 1    | 42.5±3.01        | 42.8±1.41 | 36.6±2.045 | 27.35±2.55 | 22.12±1.21 | 25.21±1.4  | 23.12±2.4  | 22.16±2.6  | 27.21±3.2  |  |
| 2    | 51.5±1.25        | 63.5±1.58 | 42.23±2.21 | 35.81±1.62 | 39.52±1.4  | 35.42±2.1  | 36.42±2.4  | 38.21±1.23 | 36.72±2.39 |  |
| 4    | 72.3±2.09        | 79.9±1.25 | 53.77±2.66 | 53.55±2.27 | 55.87±1.7  | 48.27±4.7  | 49.23±5.2  | 52.23±3.2  | 57.28±2.23 |  |
| 6    | 83.4±3.55        | 82±2.36   | 62.47±1.88 | 70.8±3.21  | 72.55±1.5  | 63.45±2.6  | 55.02±5.2  | 67.28±5.2  | 67.56±1.7  |  |
| 8    | 87.9±2.88        | 90±2.55   | 71.1±0.96  | 82.04±1.8  | 85.5±2.04  | 75.02±2.23 | 60.25±4.25 | 79.23±4.2  | 81.49±2.3  |  |
| 10   | 93.7±1.75        | 98.5±2.71 | 88.9±1.48  | 92.35±1.18 | 89.6±3.11  | 82.13±4.23 | 85.23±2.5  | 88.23±3.2  | 90.26±2.6  |  |

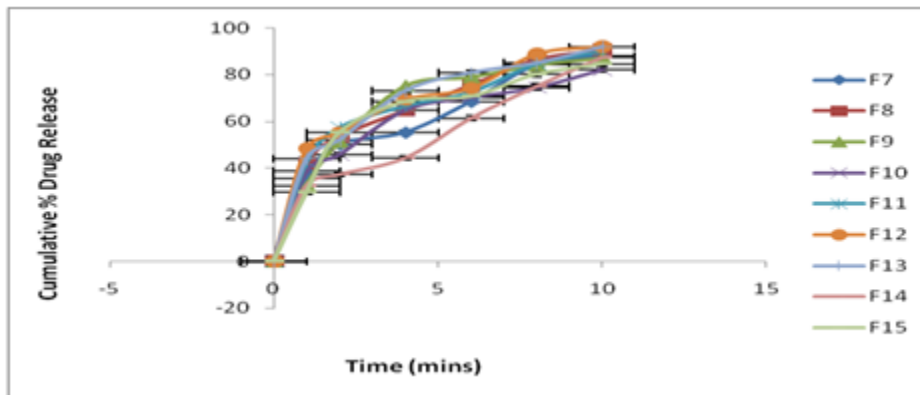


Figure 4: Cumulative Percentage Drug Release for HPMC E6 (Formulations F7-F15)

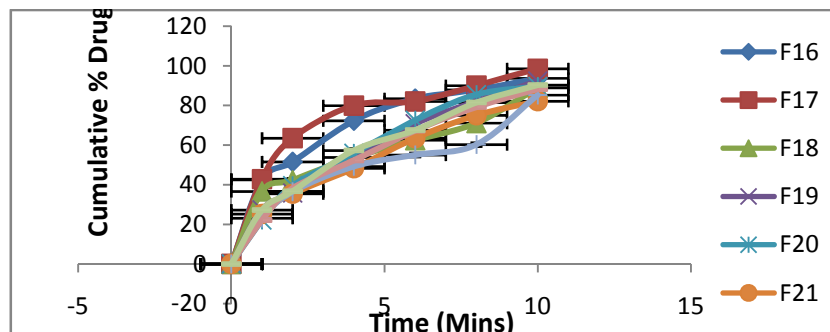


Figure 5: Cumulative Percentage Drug Release for HPMC E15 (formulations F16-24)



Comparison of optimized formulation with innovator product

From the above studies F17 was found optimum for the formulation of Eletriptan hydrobromide FDOFs. Thus cumulative drug release studies of F17 formulation tablets was compared with the marketed RELPAX-20mg film coated tablets.

Table 9: Comparison of Cumulative drug release of F17 with innovator product of RELPAX-20mg tablets

| TIME (Min)                        | 0 | 1         | 2         | 4         | 6       | 8       | 10        |
|-----------------------------------|---|-----------|-----------|-----------|---------|---------|-----------|
| F17                               | 0 | 42.8±1.41 | 63.5±1.58 | 79.9±1.25 | 82±2.36 | 90±2.55 | 98.5±2.71 |
| RELPAx-Film coated tablets (20mg) | 0 | 22±2.52   | 34±1.74   | 48±3.5    | 59±2.2  | 72±2.5  | 79.4±1.2  |

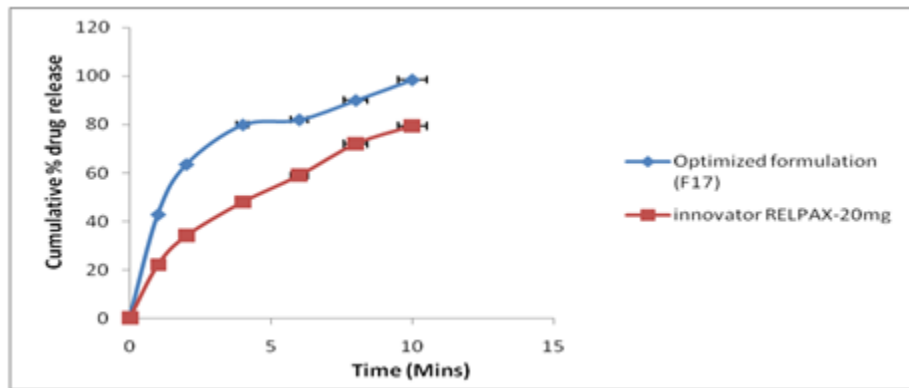


Figure 6: Comparison of Cumulative drug release of F17 with innovator product of RELPAX-20mg tablets. Drug excipient interactions studies by FTIR Spectroscopy:

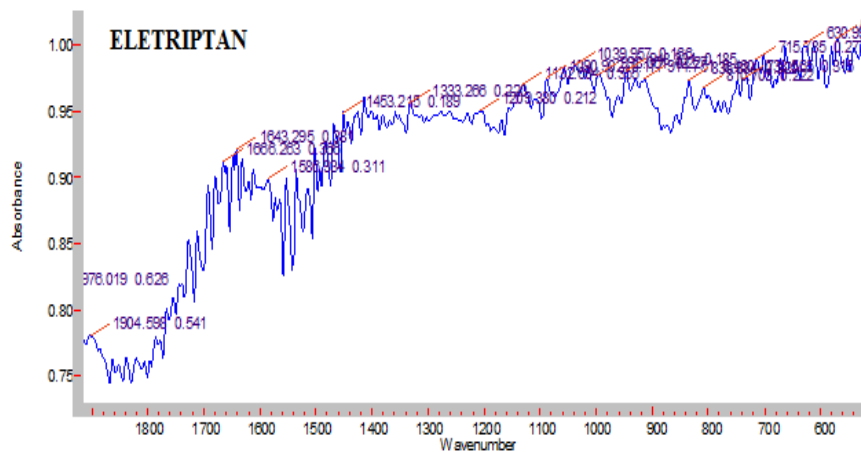


Figure 7: FTIR spectra of Eletriptan HBr pure drug



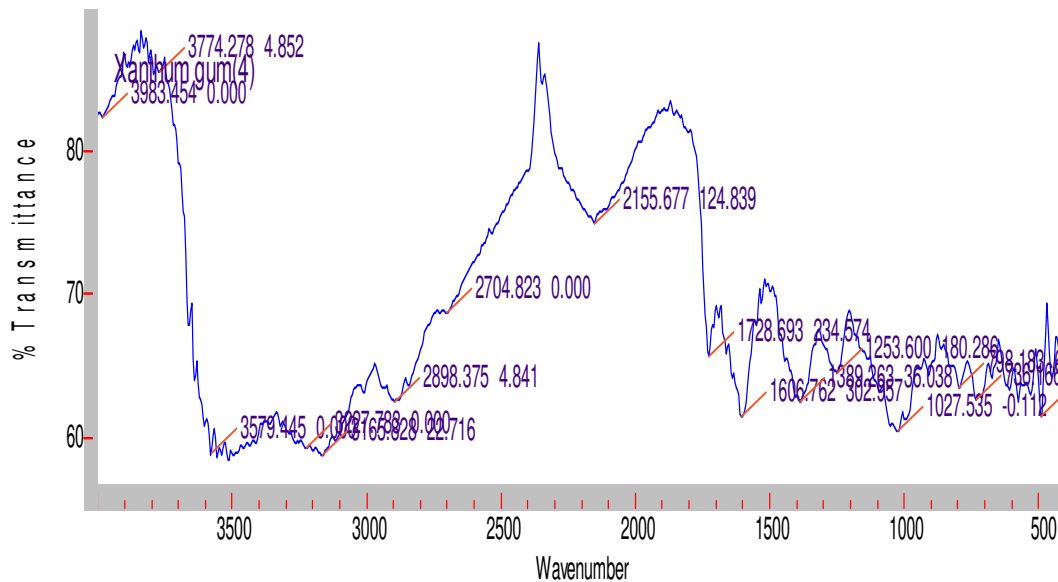


Figure 8: FTIR spectra of xanthan gum

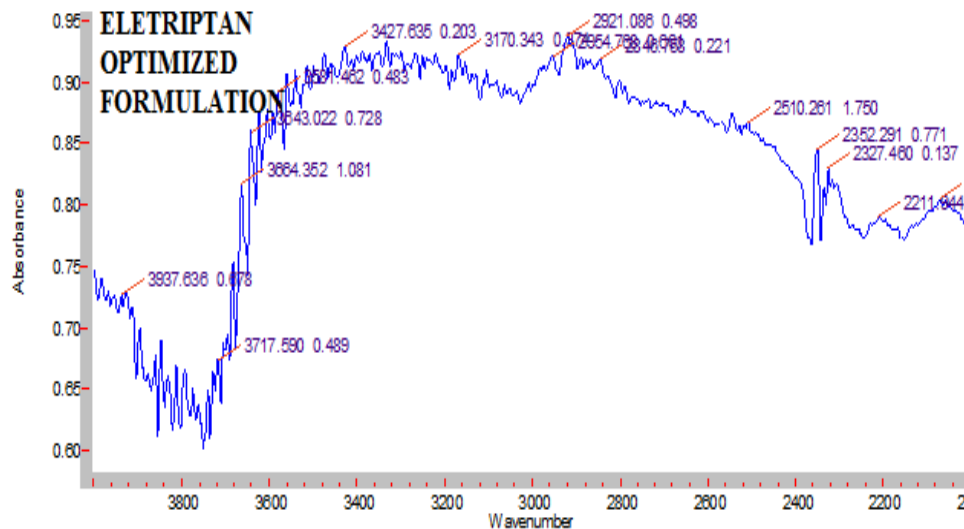


Figure 9: FTIR spectra of optimized formulation (F17)

The FTIR spectra of pure Eletriptan HBr (Figure 7) displayed band at  $1643\text{ cm}^{-1}$  due to heterocyclic  $\text{C}=\text{C}$  bond, at  $1453\text{ cm}^{-1}$  due to C-H bending, at  $1333\text{ cm}^{-1}$  due to  $\text{S}=\text{O}$ . The spectra also showed bands at  $1586\text{ cm}^{-1}$  due to N-H bending, Xanthan gum exhibited characteristic bands at  $2898\text{ cm}^{-1}$  due to C-H stretching, at  $1645\text{ cm}^{-1}$  due to Hetero cyclic  $\text{C}=\text{C}$ , at  $1452\text{ cm}^{-1}$  due to C-H bending (Figure 8), at

The FTIR spectrum of optimized formulation (Figure 9) exhibited characteristic bands consistent with the molecular structure of

Eletriptan Hydrobromide such as bands at  $2921\text{ cm}^{-1}$  due to C-H stretch, at  $1773\text{ cm}^{-1}$  due to  $\text{C}=\text{O}$  stretching, at  $3427\text{ cm}^{-1}$  due to  $\text{N}-\text{CH}_3$ , at  $1389\text{ cm}^{-1}$  due to  $\text{S}=\text{O}$ , at  $1588\text{ cm}^{-1}$  due to C-H bending. The Eletriptan HBr film formulation exhibited peaks at  $2901\text{ cm}^{-1}$  due to C-H stretching, at  $3429\text{ cm}^{-1}$  due to  $\text{N}-\text{CH}_3$ . Thus, the presence of characteristic absorption bands of Eletriptan Hydrobromide and the film containing Eletriptan Hydrobromide suggest that there is no interaction takes place between the drug and excipients used in the formulation.

### Drug excipient compatibility studies by DSC



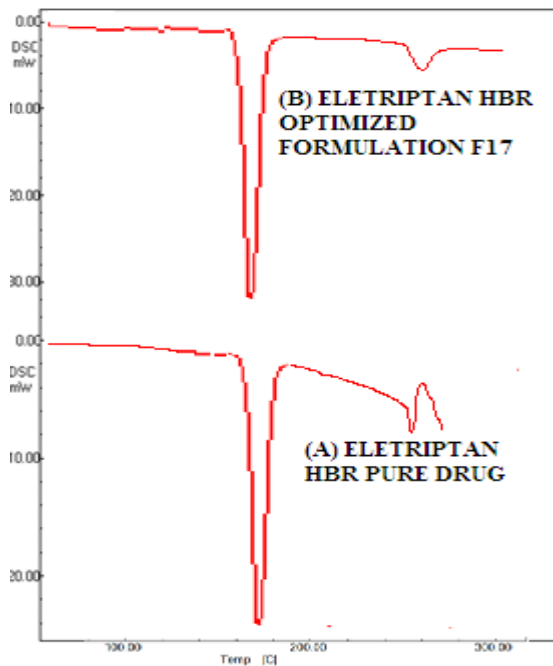


Figure 10: DSC thermogram of Eletriptan pure drug (A) and optimized formulation F17 (B)

### Interpretation of DSC Data

DSC thermograms revealed that there is no considerable change observed in melting endotherm of Eletriptan HBr pure drug (169) and optimized formulation F17 (170) (Figure 10). It indicates that there is no interaction takes place between drug and other excipients used in the formulation.

### Stability Studies for optimized formulation (F17)

Stability studies were conducted for optimized formulation (F17) for the period of 6 months according to ICH guidelines. Different parameters like disintegration time, % drug content, transparency and in vitro % drug release was evaluated. From these results it was concluded that, optimized formulation F17 is stable and retained their original properties with minor differences which depicted in Table 10.

Table 10: Physico-chemical characteristics of optimized formulation (F17) stored at  $40 \pm 2^\circ\text{C} / 75 \pm 5\% \text{RH}$

| Retest time for optimized formulation (F17) | Disintegrating Time (sec) | Percent Drug Content | In-vitro drug release profile (%) | Transparency |
|---|---------------------------|----------------------|-----------------------------------|--------------|
| 0 days                                      | $11 \pm 2$                | $98.4 \pm 0.22$      | $98.5 \pm 4.70$                   | Transparent  |
| 1 month                                     | $12 \pm 6$                | $97.86 \pm 0.14$     | $97.8 \pm 3.61$                   | Transparent  |
| 3 months                                    | $12 \pm 9$                | $97.06 \pm 0.12$     | $97.2 \pm 2.71$                   | Transparent  |
| 6 months                                    | $13 \pm 5$                | $97.54 \pm 0.26$     | $96.5 \pm 6.72$                   | Transparent  |

Pharmacokinetic study:

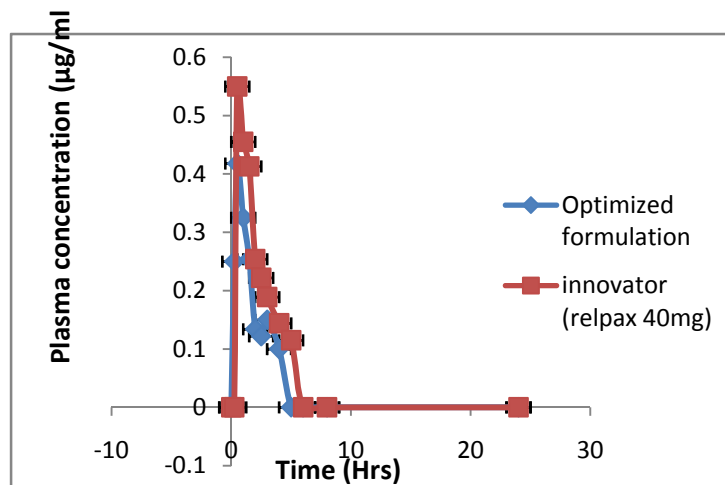


Figure 11: Plasma concentrations at different time intervals for Eletriptan Hydrobromide optimized formulation film F17 and innovator (Relpax 20mg)

Table 11: Comparison of pharmacokinetic parameters of Eletriptan Hydrobromide between the optimized formulation film F17 and innovator (Relpax 20mg) in Rabbits (mean  $\pm$  SD, n = 6).

| Parameters                        | Optimized formulation F17 | Innovator (REL PAX 20mg) |
|-----------------------------------|---------------------------|--------------------------|
| C max ( $\mu\text{g/ml}$ )        | 0.455 $\pm$ 0.1           | 0.418 $\pm$ 0.2          |
| AUC 0-t ( $\mu\text{g hr/ml}$ )   | 3.36 $\pm$ 56.44          | 3.29 $\pm$ 44.26         |
| AUC 0-inf ( $\mu\text{g hr/ml}$ ) | 3.74 $\pm$ 28.14          | 3.54 $\pm$ 38.12         |
| T max (hr)                        | 0.50 $\pm$ 1.23           | 1.0 $\pm$ 2.24           |
| t 1/2 (hr)                        | 1.253 $\pm$ 0.519         | 2.364 $\pm$ 0.01         |
| K el (hr <sup>-1</sup> )          | 1.336 $\pm$ 0.11          | 1.196 $\pm$ 0.33         |

### Bioavailability parameters

Drug release from Eletriptan Hydrobromide optimized formulation was almost similar to that from commercial formulation which was selected. Mean plasma concentration profiles of Eletriptan Hydrobromide optimized formulation and commercial formulation are presented in Figure 11. Both the formulations exhibited as immediate release *in vivo*. As compared to the innovator prepared film was showed immediate release. All the pharmacokinetics parameters displayed in Table 11. Mean time to reach peak drug concentration ( $T_{\text{max}}$ ) was 0.50 $\pm$ 1.23h and 1.0 $\pm$ 2.24h for the optimized and commercial formulations, respectively, while mean maximum drug concentration ( $C_{\text{max}}$ ) was 0.455 $\pm$ 0.2 $\mu\text{g/ml}$  and 0.418 $\pm$ 0.1 $\mu\text{g/ml}$  respectively.

### Summary and conclusion

In the present investigation, twenty five formulations of Eletriptan HBr fast dissolving oral films were prepared with HPMC E3, E6 & E15, maltodextrin, xanthan gum, propylene glycol. Formulations with HPMC E3 were not evaluated for physical parameters due to their poor film forming ability, tack property and ease of handling or peeling. The bitter taste of the drug was masked by Aspartame and Vanilla flavour. Formulations with HPMC E6 and E15 were evaluated for their physical characteristics, thickness, folding

endurance, tensile strength, disintegration time, drug content uniformity and drug release characteristics and found to be within the limits. Among the prepared formulations F17 showed minimum disintegration time 11 sec, maximum drug was released i.e. 98.5% of drug within 10 min when compared to the other formulations and finalized as optimized formulation. DSC and FTIR data revealed that no interactions takes place between the drug and polymers used in the optimized formulation. The *in vitro* dissolution profiles of marketed product (REL PAX-20mg) and optimized formulation was compared and found to be the drug released was 79.4% within 10min from the marketed product, whereas from optimized formulation (F17) the drug release was 98.5% within 10min. Therefore it can be a good alternative to conventional Eletriptan HBr tablets for immediate action. *In vitro* and *in vivo* evaluation of the Eletriptan HBr fast dissolving films confirmed their potential as an innovative dosage form to improve delivery and quick onset of action of Eletriptan HBr. Therefore, the oral fast dissolving film is considered to be potentially useful for the treatment of migraine disease where the quick onset of action is desired, also improved patient compliance.

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