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Preparation and Evaluation of Fast Dissolving Oral Film Containing Naratriptan HCl

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ABSTRACT

Recently, fast dissolving films are gaining interest as an alternative of fast dissolving tablets. The present study aimed at preparing fast dissolving oral films of Naratriptan hydrochloride as a model drug which is used for the migraine treatment. Fast dissolving dosage forms have acquired great importance in pharmaceutical industry because of their unique properties like dissolve upon contact with a wet surface, such as the tongue, within a few seconds, meaning the consumer can take the product without need for additional liquid. This convenience provides both a marketing advantage and increased patient compliance. In the present investigation various trials were carried out using two grades of HPMC (E3 and E6), Propylene glycol, PEG-400 and other polymers by solvent casting method. The prepared films were evaluated for film thickness, folding endurance, surface pH, morphological properties, % drug content and content uniformity, tensile strength, percent elongation, *in vitro* disintegration time and *in vitro* dissolution studies. The optimized formulation S11 prepared using HPMC E6 showed minimum disintegration time (10 sec), highest dissolution rate i.e. 98.23% of drug within 6 min and satisfactory physicochemical properties. Results of DSC and FTIR data of optimized formulation (S11) revealed that there was no incompatibility observed between the drug and excipients used in the formulation. These findings suggest that the fast dissolving oral film containing Naratriptan hydrochloride is considered to be potentially useful for the treatment of migraine where quick onset of action is desirable when compared with reference standard Naratrx conventional tablet.

Keywords: Naratriptan hydrochloride, fast dissolving films, solvent casting method, HPMC.

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INTRODUCTION

Oral drug delivery is the largest and oldest segment of the total drug delivery market. It is the fastest growing and most preferred route for drug administration¹. Oral ingestion has been the most convenient and commonly employed route of drug delivery². The peroral application is an effective and inexpensive way for drugs that can be absorbed in the gastrointestinal tract. The conventional dosage forms given by this route including tablets and capsules suffers from patient non-compliance due to difficulty in swallowing associated with their use. Moreover, the delay in onset of action by this route also calls for a delivery system which could provide a rapid onset and a quick relief³. For the last two decades there has been an enhanced demand for more patient-compliant dosage forms. The demand for their technology also increased drastically. A film or strip can be defined as a dosage form that employs a water-dissolving polymer, which allows the dosage form to quickly hydrate, adhere, and dissolve when placed on the tongue to provide rapid local or systemic drug delivery. Drug release may be either quick i.e. within seconds or slower to take few minutes by varying the rate of dissolution of the films⁴.

Mouth dissolving oral films offers an attractive route for systemic drug delivery. The improved systemic bioavailability results from bypassing first pass effect and better permeability due to a well supplied vascular and lymphatic drainage, also large surface area of absorption, easy ingestion & swallowing, pain avoidance make the oral mucosa a very attractive and feasible site for systemic drug delivery⁵. The delivery system consist of a very thin oral strip, which is simply based on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto site of application. It then disintegrates and dissolves to release the medication⁶. Rapidly dissolving dosage forms are also called as quick dissolving delivery systems, quick disintegrating, mouth dissolve dosage forms or melt-in-mouth dosage forms. A fast dissolving film is a novel approach to get quick onset of action and to get immediate relief of the symptoms. Hence, fast dissolving films are the best formulations as they are soluble in saliva with in 1 minute releasing the drug and inactive ingredients⁷. Bioavailability of drug in film dosage form is greater than the convectional dosage form⁸.

Migraine is a chronic, episodic, neurological disorder, which usually begins in childhood, adolescence or early adult life, characterized by unilateral headache often accompanied by nausea and vomiting⁹, gastrointestinal disturbance and extreme sensitivity to light and sound¹⁰. 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 men¹¹.

Naratriptan hydrochloride is approved for acute oral migraine therapy. The drug is a selective agonist of 5-hydroxytryptamine₁ (5-HT₁) receptors, so it used in treatment of migraine attack and as well as in nausea, vomiting and headache. Although naratriptan hydrochloride tablets have been shown to be well tolerated in the acute treatment of single migraine attacks, the tolerability and efficacy of naratriptan hydrochloride tablets with long-term is not satisfactory¹². In the present study an attempt was made to prepare oral dissolving films of naratriptan hydrochloride with the dose of 1mg in order to improve the quick on set of action and patient compliance with hydroxy propyl methyl cellulose and other excipients.

MATERIALS AND METHODS

Materials

Naratrex 1mg tablet was purchased from Sun Pharma, Mumbai. Naratriptan hydrochloride was obtained as a gift sample from Matrix laboratories, Hyderabad, India. Hydroxy Propyl Methyl Cellulose (HPMC E3 & E6) were obtained from Nectar life sciences, Hyderabad, Vanilla and Aspartame was obtained from MSN labs, Hyderabad, Propylene glycol, PEG-400, Citric acid and other excipients were purchased from SD FINE CHEM LTD, Mumbai.

Determination of dose of drug

Dose to be incorporated in each 4cm² film = 1mg of Naratriptan HCl.

Area of Petri Plate (Πr^2) = 3.14*4.5*4.5 = 63.5cm²

No. of 4cm² films obtained from main film = 9 films each with area 4cm²

Area of the main film considered (9 films) = 1*b = 6*6 = 36cm²

Area not considered = total area-area considered = 63.5-36 = 27.5cm²

Amount of drug in the area considered = 9*1 = 9 mg

Amount of drug in area not considered = 27.5*1/4 = 7mg

Total amount of drug to be incorporated into a film of 63.5cm² = amount of drug in area considered + amount of drug in area not considered = 9+7 = 16mg of Naratriptan HCl.

Preparation of Naratriptan hydrochloride oral dissolving films

The fast dissolving oral films of Naratriptan hydrochloride using polymers were prepared by solvent casting method. Hydroxypropylmethyl cellulose (HPMC) with different grades like HPMC E3 and E6 is known for its good film forming properties and has excellent acceptability. Propylene glycol as plasticizer, Citric acid as saliva stimulating agent, Aspartame as sweetening agent and Vanilla was used as a flavoring agent. The aqueous dispersion was prepared by dissolving HPMC, maltodextrin in distilled water maintained at 70°C. The suspension was used

after 24 h to remove all the air bubbles entrapped. The active ingredient was added in the required quantity. Then remaining ingredients were added in the proportions given in Table 1. The solution was poured on petri plate and then kept for drying at 60°C for first 30 min and then it was decreased to 45°C for next 24 h. The resultant film was cut into the dimension of 2 × 2 cm in size, in which 1 mg of Naratriptan hydrochloride was included¹³.

Table 1: Composition of Naratriptan hydrochloride fast dissolving oral films

Ingredients(mg & ml)	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12
Naratriptan	16	16	16	16	16	16	16	16	16	16	16	16
HPMC E3	500	450	400	350	300	280	--	--	--	--	--	--
HPMC E6	-	--	--	--	--	--	500	450	400	350	300	280
Propylene glycol	80	-	80	-	60	-	120	-	80	-	90	-
PEG-400	-	80	-	80	-	60	-	120	-	80	-	90
Glycerol	-	-	-	-	25	-	-	-	-	-	25	25
Aspartame	15	15	15	15	15	15	15	15	15	15	15	20
Citric acid	10	10	10	10	-	10	10	10	-	10	10	10
Vanilla	q.s											
Ethanol (50% v/v)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Water	q.s											

Evaluation of fast dissolving 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 and content uniformity, tensile strength, percent elongation, In vitro disintegration time and In vitro dissolution studies.

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 30 sec. 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 done¹⁴.

Film 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 calculated¹⁵.

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 (6.25 cm²) 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 reported¹⁶.

Drug content uniformity

Three films (4 cm² 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 231 nm and the drug content was calculated¹⁷.

Percent Elongation

This mechanical property was evaluated using the Instrum Universal testing instrument (Model F. 4026, Instron Ltd., Japan) with a 5 kg load cell. The percentage increase in the length of a film (L₂), 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 L₁, the increase in length is (L₂-L₁). It is measured in terms of percentage. Percent elongation and tensile strength was carried for only 4 best formulations.

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

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. Film strip of dimension 5 × 2 cm² 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 below¹⁸:

Tensile strength = Load at Failure/ Strip thickness X 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 disintegrated¹⁶.

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 Naratriptan hydrochloride was carried out using USP dissolution testing apparatus-1 (basket type) containing 300 ml of the phosphate buffer pH 6.8. The film was placed in the basket, maintained at $37 \pm 0.5^\circ\text{C}$ and the agitation speed was 50 rpm. Aliquots (5 ml) of the dissolution medium were withdrawn at 1,2,4, 6,8,10 and 12 minutes time intervals and the same amount was replaced with the fresh medium. Samples were assayed spectrophotometrically at 223 nm. The cumulative percentage drug release was calculated¹⁹.

Drug Excipient Compatibility Studies

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

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. Accurately weighed samples were placed on aluminium plate, sealed with aluminium lids and heated at a constant rate of $5^\circ\text{C}/\text{min}$, over a temp. range of 0 to 250°C .

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 spectra of the samples were prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at pressure of seven to ten tons.

Stability studies

The stability study of the formulated 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 at $2-8^\circ\text{C}$ (45% RH), $25-30^\circ\text{C}$ (60% RH), and $45-50^\circ\text{C}$ (75% RH) for a period of 45 days. The patches were characterized for the drug content and other parameters during the stability study period¹⁶.

RESULTS AND DISCUSSION

Physical characterization of FDOFs

Physical characterization of FDOFs was carried out by visual inspection and the following observations were made. All the formulations (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. Formulation S1 to S4 were found to be brittle in nature. Formulation S6 was too soft and difficult to handle,

Table 2: Evaluation of mouth dissolving films

Formulation code	Weight variation(mg)	Thickness (mm)	Folding endurance (count)	Surface pH
S1	37.00±2.1	0.14±0.00	21±3	6.71±0.05
S2	39.67±1.7	0.15±0.02	62±1	6.88±0.01
S3	40.33±1.9	0.14±0.01	76±3	6.77±0.00
S4	39.36±1.2	0.14±0.01	81±4	6.87±0.01
S5	40.66±0.5	0.14±0.03	84±1	6.93±0.02
S6	42.33±1.9	0.13±0.01	91±2	6.74±0.02
S7	41.37±0.3	0.09±0.02	82±3	6.89±0.02
S8	39.00±2.1	0.09±0.01	112±1	6.90±0.02
S9	35.66±1.6	0.05±0.03	20±2	6.86±0.03
S10	35.33±0.9	0.04±0.01	21±1	6.71±0.05
S11	30.9±1.8	0.1±0.02	90±2	6.80±0.02
S12	35.2±.9	0.1±0.01	81±3	6.89±0.02

Various trials were carried out to optimize the formula for the preparation of the films. The optimized films were evaluated for the following parameters.

Surface pH

Surface pH of all mouth dissolving films prepared by different polymers was found to be in the range of 6.7 to 6.9 pH, which was close to the neutral pH, which indicated that films may have less potential to irritate sublingual mucosa & hence, more acceptable by the patients (Table 2).

Weight variation and thickness

A result showed that as the conc. of polymer increases weight of film also increases. The weight variation of the formulations was in the range of 30.9±1.8 to 42.33±1.9 mm, which was acceptable. Thickness of mouth dissolving film depends on the conc. of polymer. Thickness of all mouth dissolving film was measured with digital vernier caliper showed thickness value in range of 0.04±0.01 to 0.15 ± 0.02 mm .

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 20±2 to 112±1, where the results are summarized in Table 2. The optimized film (S11) has folding endurance value of 90±2, which was desirable.

Drug content uniformity

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 96.6±1.1 to 100.4±0.2%, for three different cuts from each film, results were shown in Table 3. 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.

Table 3: Drug content in naratriptan hydrochloride fast dissolving oral films (4 cm²)

Formulation code	Concentration in mg	Drug content (%)
S5	1.007	97.4±0.2
S7	1.03	98.3±0.3
S8	1.003	99.5±0.1
S9	.998	96.6±1.1
S10	1.03	100.2±0.9
S11	1.018	100.4±0.2
S12	1.0076	98.3±0.3

Percent Elongation and Tensile strength:

The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters, tensile strength and elongation at break. Tensile strength and percent elongation of all prepared formulations were shown in Table 4. Results revealed that optimized formulation (S11) showed better tensile strength (11.2 g/cm²) and moderate % elongation (9.8). From the result shown in Table 4, it is clear that when the concentration plasticizer increases tensile strength and % elongation of mouth dissolving film also increases.

Table 4: Tensile strength and percent elongation of better FDOF formulations

Formulation code	Tensile strength(g/cm ²)	Percent elongation
S1	4.2	5
S7	10.9	6.2
S8	6.3	7.5
S11	11.2	9.8
S12	10.6	9.2

In vitro disintegration studies

The disintegrating time of all the formulations was ranges from 10±2 to 25±2 sec, the results were depicted in Table 5. The disintegration time of optimized formulation (S11) was found to be 10 sec, which was very less and desirable for quick onset of action.

Table 5: In vitro disintegration time of naratriptan hydrochloride FDOF batches

Formulation Code	In-vitro disintegration time(sec)
S1	25±2
S7	17±2
S8	13±2

S9	16±2
S10	18±2
S11	10±2
S12	14±2

In vitro drug release studies

Cumulative % drug release was calculated on the basis of drug content of Naratriptan hydrochloride present in the respective film. The results obtained in the in vitro drug release for the formulations were tabulated in Table 6. The graphs are depicted in Figure 1. Formulation S1, S5, S7, S8, S9, S10 and S12 shows drug release up to 79.8 ± 1.2 , 82.56 ± 1.9 , 86.6 ± 1.1 , 87.92 ± 1.9 , 90.27 ± 1.6 , 93.6 ± 1.1 and 90.27 ± 1.6 respectively at the end of 12 min. The optimized formulation (S11) was shown rapid and highest percentage of drug release i.e. 98.23 ± 1.4 within 6 min. The drug release profile of innovator product Naratrx 1 mg conventional tablet showed 82.8 ± 1.2 within 12 min.

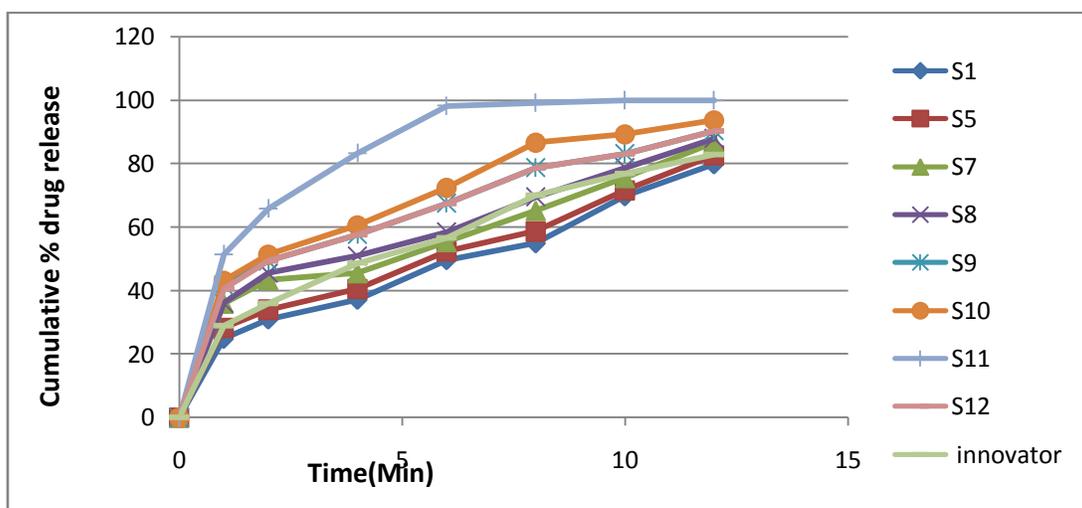


Figure 1: Cumulative % drug release of Naratriptan HCl FODF formulations

Table 6: Cumulative % drug release of naratriptan hydrochloride FDOF formulations

Time (min)	S1	S5	S7	S8	S9	S10	S11	S12	Naratrex 1mg tablet
0	0	0	0	0	0	0	0	0	0
1	24.8 ± 1.4	28.25 ± 1.4	35.9 ± 1.4	36.12 ± 1.6	41.57 ± 1.2	43.15 ± 1.0	51.46 ± 1.3	40.57 ± 1.2	28.8 ± 1.4
2	30.9 ± 1.5	33.95 ± 1.6	43.3 ± 1.7	45.51 ± 1.8	49.26 ± 1.9	51.23 ± 1.1	65.89 ± 1.5	9.26 ± 1.9	35.9 ± 1.5
4	37.1 ± 1.7	40.52 ± 1.8	45.5 ± 1.5	50.9 ± 1.2	57.61 ± 1.1	60.52 ± 1.4	83.35 ± 1.3	57.61 ± 1.1	486.1 ± 1.7
6	49.6 ± 1.9	52.29 ± 1.2	55.3 ± 1.6	58.51 ± 1.5	67.42 ± 1.0	72.36 ± 1.8	98.23 ± 1.4	67.42 ± 1.0	56.6 ± 1.9
8	54.9 ± 1.2	58.62 ± 1.8	65.2 ± 1.1	69.52 ± 1.2	78.65 ± 1.2	86.6 ± 1.9	99.16 ± 1.3	78.65 ± 1.2	69.9 ± 1.2

10	69.7 ±1.9	71.51 ±1.62	75.5 ±1.6	78.67 ±1.8	83.1 ±1.2	89.2 ±1.0	99.97 ±1.2	83.1 ±1.2	76.7 ±1.9
12	79.8 ±1.2	82.56 ±1.9	86.6 ±1.1	87.92 ±1.9	90.27 ±1.6	93.6 ±1.1	----	90.27 ±1.6	82.8 ±1.2

FTIR Studies

As shown Figure 2. it was evident that IR characteristic peaks of Naratriptan hydrochloride drug at 2962.54, 3211.79, 3733.6 cm^{-1} were prominent indicating the authenticity of the molecule and from Figure 2 and Figure 3 it was found that there was no chemical interaction.

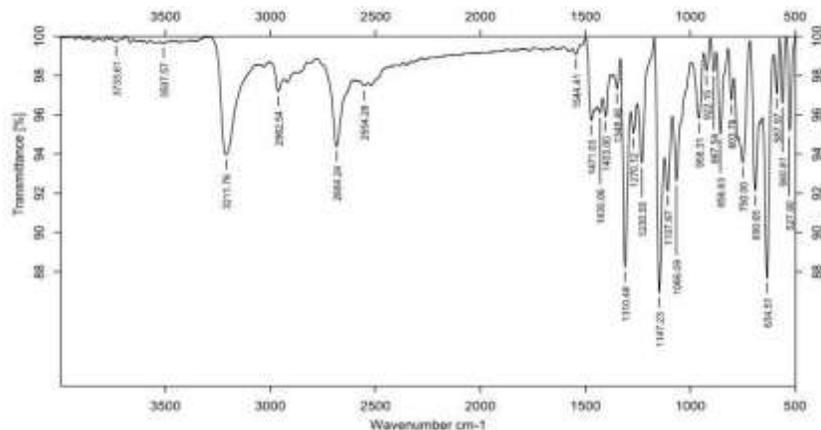


Figure 2: FTIR spectra of pure Naratriptan hydrochloride

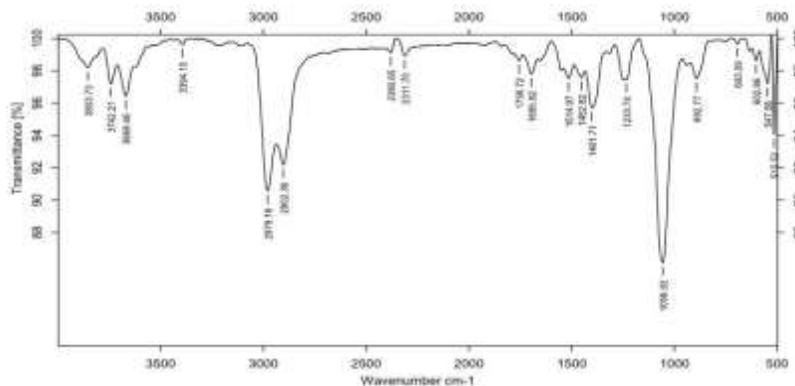


Figure 3: FTIR spectra of optimized ODF formulation (S11)

DSC studies:

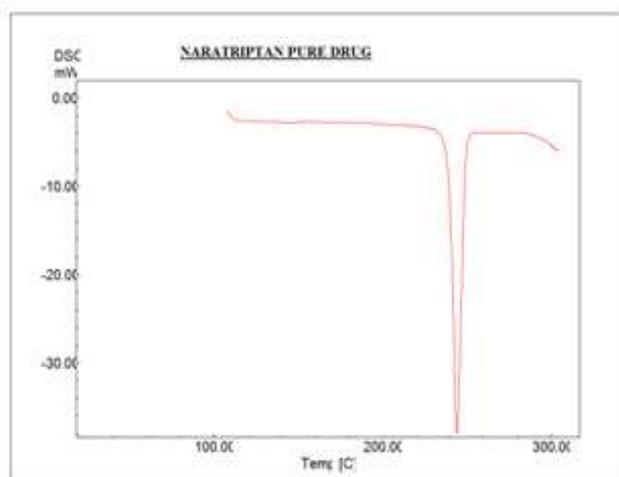


Figure 4: DSC Thermogram of naratriptan hydrochloride pure drug

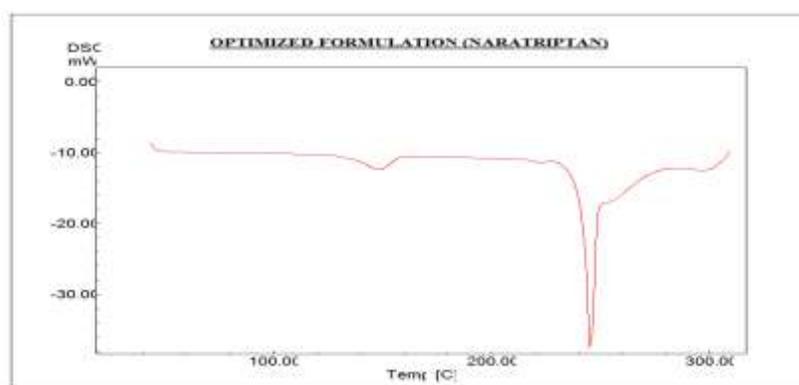


Figure 5: DSC Thermogram of optimized formulation (S11)

The DSC thermograms of the pure naratriptan hydrochloride Figure 4 and optimized formulation Figure 5 showed endothermic peaks of the pure naratriptan hydrochloride and the naratriptan hydrochloride in optimized formulation at 242.5 °C and 244.06 °C respectively. Hence no interaction between drug and polymer was observed.

Stability studies for (S11) optimized formulation

S11 formulation was selected for stability studies on the basis of high cumulative % drug release and also results of *in vitro* disintegration time. Stability studies were conducted under different conditions according to ICH guidelines. From these results it was concluded that, formulations S11 is stable and retained their original properties with minor differences. The results of disintegration time, drug content & transparency shown in Table 7 which indicates no alteration after storage.

Table 7: Accelerated stability testing data of optimized formulation (S11)

Retest Time For F23	Disintegration Time (sec)	Percent Content/ Assay (%)	Drug Transparency
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1 Week	10±3	100.4±0.2	Transparent
2 Weeks	10±5	99.8±0.6	Transparent
1 Month	10±8	99.6±0.2	Transparent
2 Months	11±0	98.7±0.4	Transparent

CONCLUSION

Fast dissolving oral films of Naratriptan HCl was formulated with different concentrations of HPMC-E3 and E6. All the formulations were evaluated for their physical characteristics, thickness, folding endurance, tensile strength, disintegration time, drug content uniformity and drug release characteristics. Among all the formulations S11 showed minimum disintegration time 10 sec and drug release was 98.23 ± 1.4 within 6 min and selected as optimized formulation. DSC and FTIR data revealed that no interactions takes place between the drug and polymers used in the optimized formulation (S11). The *in vitro* dissolution profile of marketed product (NARATRAX 1mg conventional tablet) was found to be 82.8 ± 1.2 within 12 min, when compare with optimized formulation i.e., 98.23 ± 1.4 within 6 min. Therefore it can be a good alternative to conventional Naratriptan HCl tablets. *In vitro* evaluation of the films confirmed their potential as an innovative dosage form to improve delivery of Naratriptan HCl.

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