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# Formulation and Evaluation of Naratriptan Sublingual Films

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**A B S T R A C T**

Fast dissolving sublingual films of Naratriptan was fabricated using HPMC, PVA as a film forming polymer, polysorbate 80 for fast disintegration and dissolution of the films. The prepared films were evaluated for weight variation, folding endurance, thickness, disintegration time, surface $P^H$, In-vitro dissolution studies and assay. Fast dissolving sublingual films of Naratriptan was fabricated using HPMC, PVA as a film forming polymer, polysorbate 80 for fast disintegration and dissolution of the films. Fast dissolving sublingual films of Naratriptan to treat migraine, to enhance bioavailability and avoid presystemic metabolism. The prepared films were evaluated for weight variation, folding endurance, thickness, disintegration time, surface $P^H$, In-vitro dissolution studies and assay. Fast dissolving sublingual films of Naratriptan containing HPMCE15 as the film former with 2%of polysorbate80 were found to be optimized and showed about 87.16% of drug release within 6min .The optimized formulation compared with the marketed tablet and showed rapid drug release

**Keywords:** Naratriptan, HPMC, PVA.

**A R T I C L E I N F O**

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**C O N T E N T S**



## 1. Introduction

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a laminapropria followed by the sub mucosa as the innermost layer. The oral mucosa in general is intermediate between that of the epidermis and intestinal mucosa in terms of permeability. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. There are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oralmucosa[5].

The drugs selected for films should possess good stability in saliva and water with low dose. The film should consist

of 1-25% w/w of the drug. Small dose molecules are the best candidates to be incorporated in Oral fast dissolving film. Multivitamins upto 10% w/w of dry film weight was incorporated in the films with dissolution time of less than 60seconds. It is always useful to have micronized API which will improve the texture of the film and also for better dissolution and uniformity in the oral fast dissolving films.

**Drug Profile**

Nonproprietary name: Naratriptan hydrochloride
Proprietary name : Amerge
Chemical name: N-methyl-2-[3-(1-methylpiperidin-4-yl)-1H-indol- 5yl] ethanesul fonamide
CAS number: 121679-13-8
Empirical formula: C17H25N3O2S
Molecular weight: 335.5 g/mol

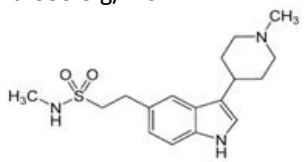

Figure 1

**Physico chemical profile**
**Density:** 1.2±0.1 g/cm3
**Melting Point:** 234-236°C

Naratriptan hydrochlorideis used to treat migraines. It helps to relieve headaches, pain and other symptoms of migraines, including sensitivity to light/sound, nausea, and vomiting.

## 2. Material & Methods

Table.1 List of chemicals

| S.N | Chemicals | Manufacturer |
|---|---|---|
| 1. | Naratriptan | Hetero drugs Ltd, Hyderabad,India |
| 2. | HPMC-E15 | Qualikems. Fine chem. Ltd, Vadodara, India |
| 3. | PVA | Lobacheimepvt Ltd, India |
| 4. | Glycerin | Qualikems. Fine chem. Ltd, Vadodara, India |
| 5. | Polysorbate-80 | Finarchemicals.Pvt.Ltd, Ahmedabad, India |
| 6. | Sodium saccharin | Qualikems. Fine chem. Ltd, Vadodara, India |
| 7. | Vanillin | Qualikems. Fine chem. Ltd, Vadodara, India |

Table 2. List of Equipment

| S.N | Equipment | Manufacturer |
|---|---|---|
| 1. | Digital weighing balance | AW 120, Shimadzu corporation Ltd, Japan |
| 2. | Magnetic stirrer | Remi equipments, Mumbai. |
| 3. | Dissolution test apparatus-11 (USP-TDT 08L) | Electrolab, TD L8, Mumbai, India |
| 4. | Cyclo mixer | Cyber lab Ltd, I NDIA. |
| 5. | UV-Visible spectrophotometer | SL 159, Elico Ltd, India. |
| 6. | Bath sonicator | Sonica soluzionitechnologi che, Millano |
| 7. | Desicator, Hot air oven | Bio Technics, India |
| 8. | Glassware | Borosil, Mumbai, India. |

**In-vitro antioxidant and free radical scavenging activity**

**Determination of λmax of Naratriptan:** 10mg of Naratriptan was dissolved in few ml of buffer, diluted suitably to obtain the absorbance in the range of 0-1and the solution was scanned at different wavelengths ranging from 200-400nmusing UV-Visible spectrophotometer to determine the λmax.

**Preparation of phosphate buffer pH6.8:**

112ml of 0.2M sodium hydroxide (8gm in 1000 ml water) was added to 250 ml of 0.2 M potassium dihydrogen phosphate (27.218 gm in 1000ml water)the volume was made up to 1000 ml using distilled water to obtain phosphate buffer pH6.8.

**Calibration curve of Naratriptan in phosphate buffer pH6.8:** 100 mg of Naratriptan was dissolved in 10 ml of buffer in a 100 ml volumetric flask and the volume was made up to 100ml using phosphate buffer from this primary stock 10ml was transferred to another volume metric flask made up to 100 ml with phosphate buffer, from this secondary stock samples were taken separately and made up to100 ml with phosphate buffer to produce 2, 4, 6, 8, 10, 12 and 14µg/ml respectively. The absorbance was measured at 226 nm by using UV Visible spectrophotometer.

**Solubility studies**

Solubility studies were performed by taken in 5ml of distilled water and different buffers of different PH in a vial (10 ml) and then excess amount of Naratriptan was added the samples placed on a shaker, agitated at room temperature for 24 hrs and aliquots were filtered. The filtered samples were assayed spectrophotometer at 230 nm. Three determinations were carried out for each sample to calculate the solubility of Naratriptan sodium. (Yogesh at al., 2007).

**Formulation of fast dissolving sublingual films**

Fast dissolving sublingual films of Naratriptan were prepared by solvent casting method which is the most common and traditional method. Different formulations (F1, F2, F3,F4, F5,F6, F7,F8)were prepared using HPMC

E15cps, PVA in different concentrations to study the effect of polymers concentration on the physico chemical properties. An attempt was also made to study the effect of polysorbent80 on drug release. Formulations were prepared with various concentrations of polymers 2%,3%, combination of polymers, without and with varying concentrations of polysorbate 80 as shown in Table 8.HPMC E-15,PVA are the film forming agents, glycerin acts as a plasticizer imparting flexibility and Sodium saccharin imparts sweetness and vanillin imparts flavor to the formulation.

**Preparation of casting solutions**

The weighed quantities of polymers were kept for swelling overnight in distilled water and dissolved (heated, if necessary). Drug was dissolved in water and added to the polymer solution. Glycerin, polysorbate80 were added to the solution and mixed using magnetic stirrer. The viscous solution was degassed using bath sonicator and the resulting bubble free solution was used for film casting.

**Preparation of fast dissolving sublingual films**

The casting solution (10ml) was poured into the petri plates and dried at 40˚c in an oven for 24hrs for solvent evaporation. The films were removed by pulling and cut into dimension of 2cm×2cm ($4cm^2$) eliminating the imperfections. These films are kept in a desiccator for 2 days further drying and wrapped in aluminium foil and packed in self- sealing cover.

**Evaluation of fast dissolving sublingual films:**

**Appearance**

All the prepared films were checked for their transparency and opacity.

**Weight variation**

$2×2cm^2$ film was cut at three different places in the cast film. The weight of each film strip was taken and then weight variation observed.

**Film thickness**

Thickness of film was measured with micrometer screw gauge at different strategic locations. This is essential to ascertain uniformity in the thickness of the films as this is directly related to the accuracy of the dose in the strip.

**Tackiness**

Six films were randomly selected. Each strip was pressed against the finger strips and tackiness was recorded. Results were noted in qualitative terms as tack and non-tacky.

**Folding endurance**

The folding endurance is expressed as the number of folds (number of times the film is folded at the same place) requied to break the specimen or to develop visible cracks. This also gives an indication of brittleness of the film. A strip of 2cm×2cm ($4cm^2$) was subjected to folding endurance by folding the patch at the same place repeatedly several times untill a visible cracks was observed and the values were reported.

**Surface pH**

The surface pH of the film was determined in order to investigate the possibility of any side effects in-vivo. The film to be tested was placed in a petri dish and was moistened with 0.5 mlof distilled water and kept for 30sec. The pH was noted after brining the electrode of the pH meter in contact with the surface of the formulation and allowing equilibrium for 1 min. The average of three determinations for each formulation was determined.

**Drug content uniformity**

A Fast dissolving sublingual films($4cm^2$)was transferred into a graduated flask containing 100ml of phosphate buffer $p^H$6.8.The solution was stirred for 1 hr on a magnetic stirrer. The solution was filtered and transferred suitable dilutions with phosphate buffer, the absorbance value was measured at 226nm and the drug content was calculated.

**Disintegration time**

The disintegration time was measured using modified disintegration method. For this purpose a petri dish was filled with 10 ml of water. The film was carefully put in the center of dish. Thefilm to completely disintegrate in to fine particles was noted.

***In vitro* dissolution studies**

*In vitro* dissolution of fast dissolving sublingual films was studied in USP basket type dissolution test apparatus using 300ml phosphate buffer $p^H$6.8 as the dissolution medium. The temperature was maintained at 37±0.5c and 50 rpm throughout the experiment.5ml sample was withdrawn at different time intervals and the same quantity was replaced with phosphate buffer of $p^H$6.8. Samples were determined using UV visible spectrophotometer at 226 nm. The absorbance values were calculated into concentration using standard graph and determine the amount of drug release.

## 3. Results and Discussion

**Determination of maximum Absorption of Naratriptan**

Absorption maximum of Naratriptan pure sample was found to be at 226nm using UV- Visible spectrophotometer.

Table 3: Absorbance values of Naratriptan in phosphate buffer pH 6.8

| Concentration (µg/ml) | Absorbance |
|---|---|
| 0 | 0 |
| 2 | 0.121 |
| 4 | 0.248 |
| 6 | 0.368 |
| 8 | 0.507 |
| 10 | 0.633 |
| 12 | 0.731 |
| 14 | 0.856 |

**Construction of calibration curve of Naratriptan in Phosphate buffer $P^H$ 6.8.**

The standard graph data of Naratriptan has shown in Table 9.The standard graph data of Naratriptan shown good linearity over a concentration range of 0-14µg/ml with $R^2$ value 0.999. The equation was y=0.0618x.This was utilized in the estimation of Naratriptan sample.

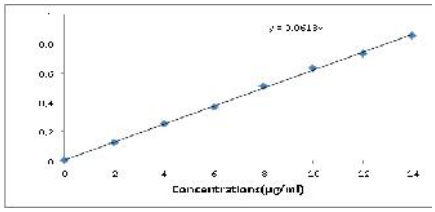

Fig 2: Calibration curve of Naratriptan in phosphate buffer pH 6.8.

Table 4: Evaluation parameters of Naratriptan fast dissolving sublingual films

| Formulation code | Appearance | Weight variation(mg) | Folding endurance | Surface $P^H$ |
|---|---|---|---|---|
| F1 | Transparent | 58±0.655 | 102±1.51 | 7.01±0.08 |
| F2 | Transparent | 53±0.563 | 129±2.27 | 6.93±0.05 |
| F3 | Transparent | 57±0.488 | 90±1.07 | 6.85±0.07 |
| F4 | Transparent | 63±0.571 | 112±2.57 | 7.04±0.02 |
| F5 | Transparent | 91±0.473 | 120±2.17 | 6.72±0.05 |
| F6 | Transparent | 96±0.514 | 113±1.93 | 6.87±0.09 |
| F7 | Transparent | 102±0.500 | 105±3.04 | 7.00±0.04 |
| F8 | Transparent | 89±0.605 | 117±2.89 | 6.91±0.01 |

Table 5: *In vitro* dissolution profiles of Naratriptan FDSFs

| Time(min) | F1 | F2 | F3 | F4 |
|---|---|---|---|---|
| 0 | 0±0 | 0±0 | 0±0 | 0±0 |
| 2 | 36.87±1.20 | 28.87±1.01 | 23.95±1.28 | 16.65±2.30 |
| 4 | 48.88±2.36 | 41.26±1.03 | 34.12±0.24 | 23.67±1.98 |
| 6 | 69.42±3.90 | 68.18±1.14 | 57.34±1.35 | 42.17±0.12 |
| 8 | 80.93±1.20 | 76.93±1.20 | 68.66±1.74 | 59.87±1.16 |
| 10 | 91.77±1.67 | 89.51±1.67 | 78.50±0.89 | 67.93±2.20 |
| 12 | 97.94±1.58 | 93.71±2.63 | 83.59±1.47 | 76.72±2.85 |
| 15 | 98.01±2.32 | 96.89±2.32 | 90.12±3.18 | 84.17±1.23 |
| 30 | 98.96±3.11 | 97.88±3.11 | 95.74±1.16 | 95.06±1.96 |

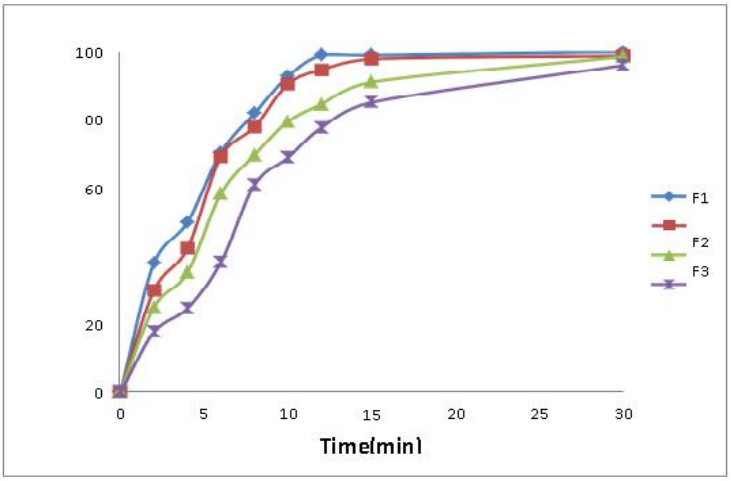


Figure 3. *In vitro* dissolution profiles of Naratriptan FDSFs

Table 6: In vitro dissolution profiles of Naratriptan FDSFs

| Time (min) | F5 | F6 | F7 | F8 |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 2 | 48.29±1.96 | 37.28±2.13 | 29.23±2.64 | 26.71±1.90 |
| 4 | 62.6±1.07 | 50.43±1.58 | 48.13±1.88 | 39.51±2.06 |
| 6 | 87.16±1.47 | 77.89±1.92 | 59.09±2.21 | 51.23±2.41 |
| 8 | 90.88±1.65 | 83.65±1.43 | 74.17±1.89 | 64.79±1.14 |
| 10 | 94.6±1.09 | 89.76±2.33 | 83.44±1.11 | 74.12±1.76 |
| 12 | 95.56±0.57 | 92.87±1.17 | 90.25±2.42 | 80.38±2.91 |
| 15 | 97.01±1.23 | 95.55±1.61 | 94.76±1.78 | 89.49±1.99 |
| 30 | 97.11±2.01 | 97.45±0.95 | 97.09±1.29 | 97.23±2.77 |

Table 7: comparison of *In-vitro* dissolution profile of optimized formulation FDSFs with Marketed product

| Time(min) | F5 | Marketed product |
|---|---|---|
| 0 | 0±0 | 0±0 |
| 2 | 48.29±1.96 | 4.13±2.36 |
| 4 | 62.6±1.07 | 19.47±1.21 |
| 6 | 87.16±1.47 | 27.14±1.03 |
| 8 | 90.88±1.65 | 33.63±1.78 |
| 10 | 94.6±1.09 | 41.57±1.66 |
| 12 | 95.56±0.57 | 52.64±1.29 |
| 15 | 97.01±1.23 | 68.61±2.44 |
| 30 | 97.11±2.01 | 72.5±2.12 |

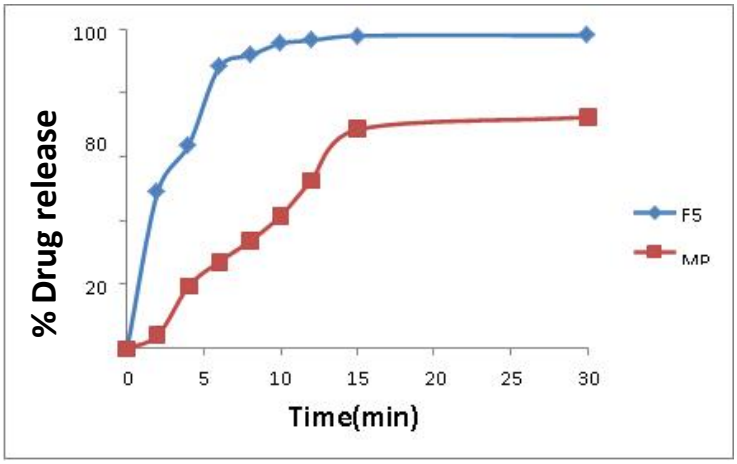


Fig 4: comparison of *In-vitro* dissolution profile of optimized formulation (FDSFs) with Marketed product

**Discussion**

The main objective of present study is to formulate and evaluate fast dissolving sublingual films of Naratriptan to enhance bioavailability and avoid presystemic metabolism. Fast dissolving sublingual films of Naratriptan was fabricated using HPMC, PVA as a film forming polymer, polysorbate 80 for fast disintegration and dissolution of the films. The prepared films were evaluated for weight variation, folding endurance, thickness, disintegration time, surface $P^H$, *In-vitro* dissolution studies and assay. The optimized formulation were compared with the marketed tablets and showed rapid drug release and the details are summarized below.

- Calibration curve of Naratriptan in Phosphate buffer $P^H$ 6.8. were plotted.
- The films were prepared using 2%and 3% of polymers i.e HPMC and PVA along with varying concentration of Polysorbate 80.
- All the prepared films were evaluated for weight variation, folding endurance and surface $p^H$, drug content, thickness, disintegration time and in vitro dissolution studies.All the films prepared were formed to be flexible, smooth, non-sticky homogenous and transparent with no visible particulate matter.
- The weight of the films varied with polymer concentration was found to be in the range of 53±0.563 to 102±0.500. The surface pH

was found to be in the range of 6.72- 7.04, which is close to the neutral pH, which indicated that the films may have less potential to irritate.

- The thickness was varied in the range of of0.64±0.087 to1.18±0.089mm. The drug content for all films were evaluated and the values were ranged from 95.83 ± 3.56 to 98.95± 2.52.No significant difference in the drug content among the films indicate good content uniformity. The disintegration time for all formulations were evaluated and the values were ranged in in55±1.50to130±2.00 sec. The disintegration time was found to increase with increase in the concentration of the polymer. Films containing HPMC E15 were found to disintegrate faster than those with PVA.
- Films formulated with varying concentration of polysorbate 80 (0% and 2%) and the formulations containing 2% polysorbate showed faster dissolution.
- Among eight formulations F5 was found to be best formulation i.e more than 85% of drug is released within 6min compared to other formulations.

**4. Conclusion**

Fast dissolving sublingual films of Naratriptan was fabricated using HPMC, PVA as a film forming polymer, polysorbate 80 for fast disintegration and dissolution of the films. Fast dissolving sublingual films of Naratriptan to treat migraine, to enhance bioavailability and avoid presystemic metabolism. The prepared films were evaluated for weight variation, folding endurance, thickness, disintegration time, surface $P^H$, *In-vitro* dissolution studies and assay. Fast dissolving sublingual films of Naratriptan containing HPMCE15 as the film former with 2% of polysorbate80 were found to be optimized and showed about 87.16% of drug release within 6min .The optimized formulation compared with the marketed tablet and showed rapid drug release

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