Formulation and *In-vitro* Evaluation of Naratriptan Hydrochloride Sublingual Tablets

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Abstract-In the present work, an attempt has been made to develop Sublingual tablets of Naratriptan hydrochloride. In the present work Sodium starch glycollate, Crospovidone and Croscarmellose sodium were employed as super disintegrating agents to enhance the solubility and dissolution rate of selected drug molecule. All the formulations were prepared by direct compression method using6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showedgood flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F4 formulation showed maximum % drug release i.e., 99.16 % in 8 min hence it is considered as optimized formulation. The F4 formulationcontains Crospovidone as superdisintegrate in the concentration of 2.5 mg.

Key Words: Naratriptan hydrochloride, Crospovidone, CroscarmelloseSodium, Sodium starch glycollate

INTRODUCTION

Sublingual delivery

Systemic delivery of drugs through the mucosal membranes lining the floor of the mouth to the systemic circulation.

Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly into the blood stream through ventral surface of the tongue and floor of the mouth. The drug solutes are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and brachiocephalic vein and then drained in to systemic circulation. Sublingual absorption is mostly rapid in action, but also short acting in duration.

ADVANTAGES OF SUBLINGUAL DRUG DELIVERY SYSTEM

1. A relatively rapid onset of action can be achieved compared to the oral route, and the formulation can be removed, if therapy is required to be discontinued.
2. The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.
3. Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
4. They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing(1).

DISADVANTAGES OF SUBLINGUAL DRUG DELIVERY SYSTEM

1. Since sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.
2. Although this site is not well suited to sustained drug delivery systems.
3. Sublingual medication cannot be used when a patient is uncooperative or unconscious.
4. The patient should not smoke while taking sublingual medication, because smoking causes vasoconstriction of the blood vessels.

This will decrease the absorption of the medication.

METHODOLOGY

PREPARATION OF CALIBRATION CURVE OF NARATRIPTAN HYDROCHLORIDE

100mg of Naratriptan hydrochloride was dissolved in 100ml of phosphate buffer pH 6.8 to give a concentration of 1mg/ml (1000µg/ml). From the above standard solution (1000µg/ml), 10 ml was taken and diluted to 100ml with phosphate buffer pH 6.8 to give a concentration of 100µg/ml. From this stock solution, aliquots of 0.2, 0.4, 0.6, 0.8 and 1ml were pipetted out in 10ml volumetric flask and the volume was made up to the mark with phosphate buffer PH 6.8 to produce concentration of 2, 4, 6, 8 and 10 µg/ml respectively. The absorbance (abs) of each concentration was measured at respective (λmax) i.e., 259 nm [(2)].

FORMULATION DESIGN:

The sublingual tablets containing 2.5 mg of Naratriptan hydrochloride were prepared by direct compression method and various formulations used in the study are shown in below table with total weight of 60 mg.

Table:1 Formulation chart

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Naratriptan hydrochloride(mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sodium starch glycolate (mg)	2.5	5	7.5	-	-	-	-	-	-
Crospovidone (mg)	-	-	-	2.5	5	7.5	-	-	-
Croscarmellose sodium (mg)	-	-	-	-	-	-	2.5	5	7.5
Magnesium stearate (mg)	2	2	2	2	2	2	2	2	2
Talc (mg)	2	2	2	2	2	2	2	2	2
Microcrystalline cellulose (mg)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total weight (mg)	60	60	60	60	60	60	60	60	60

FORMULATION OF SUBLINGUAL TABLETS OF NARATRIPTAN HYDROCHLORIDE BY DIRECT COMPRESSION METHOD:

- The drug, disintegrant, diluents were weighed and passed through 40mesh.
- All the above ingredients were co-ground and properly mixed together.
- Magnesium stearate was passed through sieve number 40, mixed and blended with the initial mixture in a polybag.
- The lubricated blend was compressed into tablets using rotary tablet machine-8 station with 6mm flat punch, B tooling.
- Each tablet contains 2.5 mg Naratriptan hydrochloride and other pharmaceutical ingredients. Total weight of tablet was found to be 60mg [(3)]

EVALUATION OF PRECOMPRESSIONAL PARAMETERS

Flow properties:

Angle of Repose:

It is performed to determine the flow rate of powder done by the funnel method. The powder was poured into a funnel which is fixed from height of 2cm of the plane surface. Circumference was drawn with a pencil on the graph paper and the radius of base of a pile was measured at 5 different points and average was taken for calculating Angle of repose using following equation [(4)]:

$$\text{Angle of repose } (\Theta) = \tan^{-1}(h/r)$$

Where as,

H=height of the pile, R=radius of the pile.

Angle of Repose less than 30 shows the free flowing property of the material.

Bulk Density:

Bulk density was determined by pouring a weighed quantity of tablet blend into graduated cylinder and measuring the height. Bulk density is the ratio of mass of tablet blend to bulk volume.

$$\text{Bulk density} = M / Vo$$

Where,

M = weight of powder, Vo = bulk volume.

Tapped density:

Tapped density is the ratio of mass of tablet blend to tapped volume of the tablet blend. Accurately weighed amount of tablet blend poured in graduated cylinder and height is measured.

Then cylinder was allowed to 100 tapping under its own weight on to a hard surface. The tapping was continued until no further change in height was noted.

$$\text{Tapped density } Do = M / V_f$$

Where,

M = weight of the powder Vf = final volume.

Hausner's ratio:

The Hausner's ratio indicates the flow properties of powder and measured by the ratio of tapped density to bulk density. Hausner's ratio is determined by the given formula.

$$\text{Hausner's Ratio} = \text{tapped density} / \text{bulk density}$$

Hausner's Ratio

H=Vf/Vo

Where,

Vo is the initial volume. Vf is the final volume.

Carr's index:

Compressibility is the ability of powder to decrease in volume under pressure. Using bulk density and tapped density the percentage compressibility of powder were determined, which is given as carr's compressibility index. It is indirectly related to the relative flow rate. Carr's compressibility index was determined by the given formula.

$$C = (Vo-Vf)/ Vf\times100$$

Where,

Vo is the bulk density, Vf is the tapped bulk density

A Carr's index greater than 25 is considered to be an indication of poor flowability, and below 15 is considered to be an indication of good flowability.

Table:2 Acceptance criteria of flow properties

Flow properties	Angle of repose	Compressibility Index (%)	Hausner's ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	>66	>38	>1.6

EVALUATION OF TABLETS [5,6]:

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quantity. There are various standards that have been set in the various pharmacopeias regards the quality of pharmaceutical tablets and that includes the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters.

POST COMPRESSION PARAMETERS:

Physical appearance:

The tablets were examined under a lens for the shape of the tablet and colour by keeping the tablets in light.

Tablet size and Thickness:

Randomly 10 tablets were taken from formulation batch and their thickness (mm) was measured using a Vernier callipers.

Weight variation test:

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The percentage deviation in weight variation is shown in table.

Table: 3 Limits of Weight variation

Average Weight of Tablet (mg)	% deviation
130mg or less	10
> 130or <324	7.5
> 324	5

Hardness test:

The hardness of the tablets was determined by using Monsanto hardness tester. It is expressed in Kg/cm^2. Six tablets were randomly picked from each formulation.

Friability test:

It is the phenomenon whereby tablet surfaces are

damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche friabilator (Lab India, FT 1020). It is expressed in percentage (%). Ten tablets were initially weighed and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again. The percentage friability was then calculated by.

% friability = initial weight – final weight / initial weight

Drug Content estimation:

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch.

Four tablets were weighed and crushed in the mortar. The powder equivalent to 1.25 mg of the drug were weighed and dissolved in 100ml phosphate buffer pH 6.8 to give a concentration of 12.5 µg/ml. 2ml of this solution was taken and diluted to 10ml to give a concentration of 2.5µg/ml. The absorbance of the prepared solution was measured at 259nm using UV Visible spectrophotometer (Lab India, UV-3200).

Disintegration test:

The first important step is break down of tablet into smaller particles or granules, a process known as disintegration. The USP device used to test disintegration uses 6 glass tubes that are 3inches long, open at the top and held against a 10 mesh screen at the bottom end of the basket rack assembly. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a one liter beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2^0C, such that the tablets remain 2.5cm below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker. A standard motor- driven device is used to move the basket assembly containing the tablets up and down through a distance of 5 to 6 cm, at a frequency of 28 to 32 cycles per minute. Perforated plastic discs may also be used in the test [7,8].

Uncoated USP tablet have disintegration time standards as low as 5 min, but the majority of the tablets have a maximum disintegration time of 30 min. Enteric coated tablets show no evidence of disintegration after 1 hour in simulated gastric fluid. The same tablets are then tested in stimulated fluid and are used to disintegrate in 2 hours as the time specified in the monograph.

In -vitro dissolution studies [9, 10]:

In-vitro release studies were carried out using a modified USP XXIII dissolution test apparatus (Lab India, DS-800).

The dissolution fluid was 500ml of phosphate buffer pH 6.8 at a speed of 50 rpm at a temperature of 37^0 c were used in each test. Sample of dissolution medium (5ml) were withdrawn for every 2min and assayed for Naratriptan hydrochloride by measuring absorbance at 259 nm. For all the 5ml of the test medium were collected at specified time intervals and replaced with same volume of phosphate buffer pH 6.8.& maintained conditions are.

Apparatus used	:	USP II Lab India DS 800
Dissolution Medium	:	Phosphate buffer pH 6.8
Dissolution Medium volume	:	500ml
Temperature	:	37^0C
Speed of paddle	:	50rpm
Sampling Intervals	:	1,2,3,4,5,6,7,8 minutes.
Sample withdrawn	:	5ml
Absorbance measured	:	259 nm

Stability studies:

The purpose of stability testing is to provide the evidence for the quantity of drug substance or drug product, and how it varies with time under the influence of environmental condition (heat, humidity, light, air etc). The final formulation was packed in suitable packing like blister or strip packs and then they will be kept at different temperature, humidity conditions and the samples will be analyzed for their physical and chemical properties [11].

Table: 4 ICH guidelines for stability study:

Study	Storage conditions	Time period
Accelerated	40^0c ± 2^0 c / 75% ± 5 % RH	6 months
Intermediate	30^0c ± 2^0 c / 65% ± 5 % RH	6 months
Long term	25^0c ± 2^0 c / 60% ± 5 % RH	12 months

RESULTS AND DISCUSSIONS

Standard Calibration curve of Naratriptan hydrochloride:

Table:5 Concentration and absorbance obtained for calibration curve of Naratriptan hydrochloride in pH 6.8 Phosphate buffer.

S. No.	Concentration (µg/ml)	Absorbance (at 259 nm)
1.	0	0
2.	1	0.0432
3.	5	0.133
4.	10	0.269
5.	15	0.397
6.	20	0.509
7.	25	0.671

It was found that the estimation of Naratriptan hydrochloride by UV spectrophotometric method at λmax 259nm in pH 6.8 Phosphate buffer had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2- 10µg/ml. The regression equation generated was $y = 1.180x + 0.017$, $R^2 = 0.996$

Pre-compression parameters:

The data's were shown in Table 8 The values for angle of repose were found in the range of 25°-30°.

Bulk densities and tapped densities of various formulations were found to be in the range of 0.41 to 0.50 (gm/cc) and 0.50 to 0.58 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 13.06% to 18.18%. The Hausner' ratio fall in range of 1.14 to 1.22. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Table:6 Pre-compression parameters

Formulations	Bulk density (gm/cm^2)	Tap density (gm/cm^2)	Carr's index (%)	Hausner ratio	Angle of repose (θ)
F1	0.45	0.55	18.18	1.22	27.91
F2	0.47	0.55	14.54	1.17	28.23
F3	0.50	0.58	13.79	1.16	29.34
F4	0.46	0.55	16.36	1.19	26.79
F5	0.50	0.58	13.79	1.16	29.34
F6	0.47	0.55	14.54	1.17	28.22
F7	0.50	0.58	13.79	1.16	29.34
F8	0.41	0.50	18	1.21	26.78
F9	0.41	0.50	18	1.21	26.78

Weight variation test:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 6. The average weight of the tablet is approximately in range of 98 to 105.5mg, so the permissible limit is ±10% (=100mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit[12,13].

Hardness test:

Hardness of the three tablets of each batch was checked by using Monsanto hardness tester and the data's were shown in Table 6. The results showed that the hardness of the tablets is in range of 2.5 to 3.00 kg/cm2, which was within IP limits.

Post-Compression parameters:

Thickness:

Thickness of three tablets of each batch was checked by using Vernier Caliper and data were shown in Table 6. The result showed that thickness of the tablet is raging from 1.56 to 1.64.

Friability:

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 6. The average friability of all the formulations lies in the range of 0.30 to 0.51% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

In-vitro disintegration time:

Tablets of each batch were evaluated for *in-vitro* disintegration time and the data's were shown in the Table 6. The results showed that the disintegration time of prepared tablets were in the range of 12.66 to 30.33 seconds.

Table: 7 Post- Compression parameters:

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Disintegration time (sec)	Friability (%)	Assay (%)
F1	60	2.5	2.34	60	0.43	97.23
F2	62	2.6	2.24	62	0.34	98.55
F3	59	2.5	2.29	72	0.49	98.16
F4	61	2.6	2.28	69	0.47	99.34
F5	62	2.3	2.39	70	0.49	98.16
F6	63	2.7	2.24	62	0.34	98.55
F7	62	2.5	2.29	70	0.49	98.16
F8	60	2.6	2.36	67	0.34	99.25
F9	62	2.5	2.26	67	0.34	99.25

Assay:

Assay studies were performed for the prepared formulations. From the assay studies it was concluded that the all formulations were showing the % drug content values within 97.23 -99.2%.

In-vitro Dissolution studies:

In-vitro dissolution studies were carried out by using 500ml of pH 6.8 Phosphate buffer in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 30 min.

Table: 8 *In-vitro* dissolution studies of all formulations.

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	15.46	10.83	49.72	24.37	31.73	18.35	28.45	39.50	12.51
2	26.63	26.72	60.16	31.68	34.56	22.90	35.28	46.35	26.38
3	35.64	36.16	68.15	49.37	41.91	38.71	48.90	56.28	35.17
4	40.38	47.46	72.56	58.35	62.48	50.16	66.83	69.71	47.37
5	46.44	58.57	78.41	74.37	89.19	64.32	78.17	76.26	54.96
6	53.64	68.25	83.27	88.18	99.50	76.42	82.45	80.14	62.56
7	69.82	73.19	87.45	94.65	-	80.14	87.16	85.26	78.35
8	80.56	90.16	94.26	99.16	-	92.46	92.18	91.28	89.26

From the tabular column 10 it was evident that the formulations prepared with super disintegrate Crospovidone showed maximum % drug release in 8 min i.e 99.16% (F4 formulations and the concentration of super disintegrate was 2,5 mg). So the principle of super disintegrates was found to be useful to produce Sublingual tablets. F4 formulation was considered as optimized formulation.

FTIR GRAPHS:

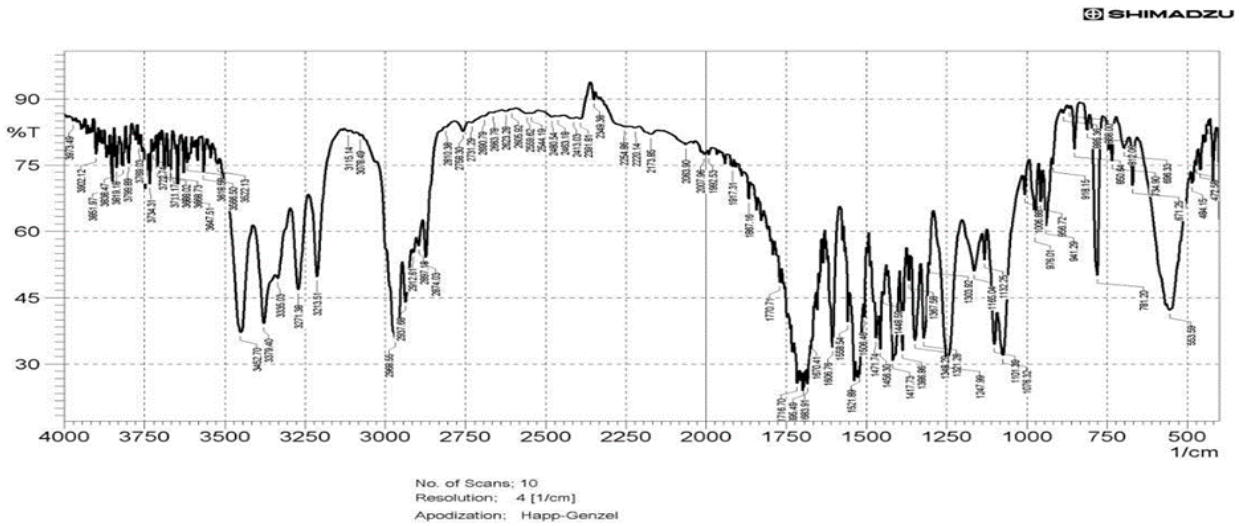

Figure: 1 FTIR spectrum of optimized formulation(F4)

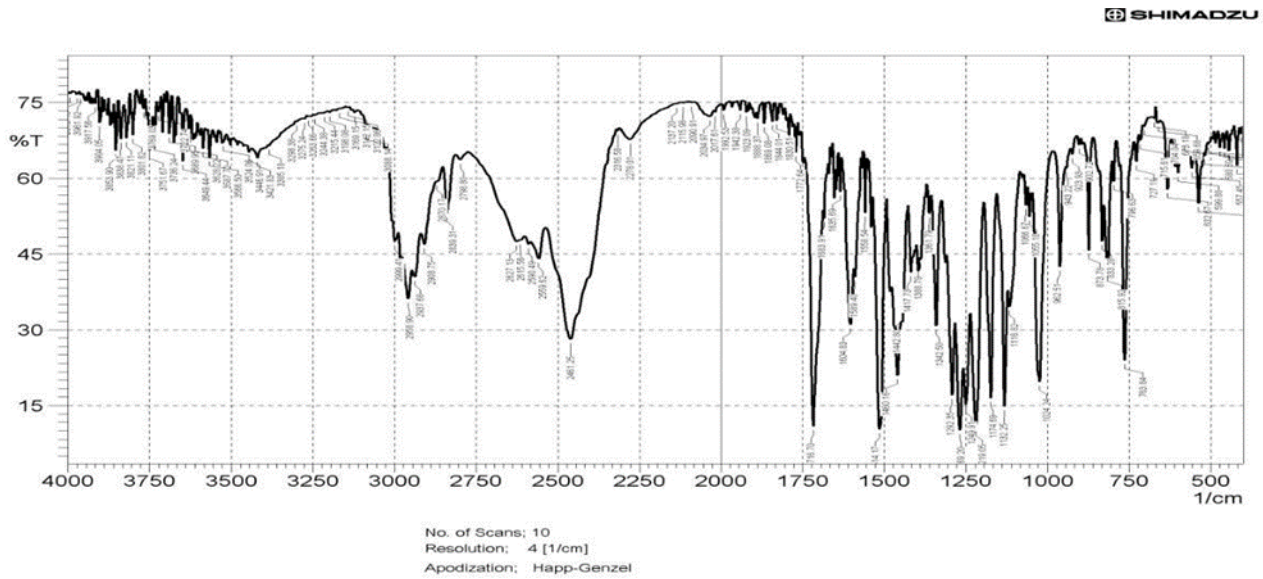

Figure: 2 FTIR Spectrum of pure drug.

CONCLUSION

In the present work, an attempt has been made to develop Sublingual tablets of Naratriptan hydrochloride. In the present work Sodium starch glycollate. Crospovidone and Croscarmellose sodium were employed as super disintegrating agents to enhance the solubility and dissolution rate of selected drug molecule. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F4 formulation contains Crospovidone as super disintegrate in the concentration of 2.5 mg showed maximum % drug release i.e., 99.16 % in 8 min hence it is considered as optimized formulation.

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