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Original Research Article

Development and Evaluation of Mouth Dissolving Tablet of Taste Masked Naratriptan HCL using Sublimation Technique

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Abstract

The aim of current study was to develop simple and convenient dosage form for delivery of naratriptan hydrochloride. Mouth dissolving tablets of Naratriptan HCl were prepared using superdisintegrants Croscarmellose sodium, sodium starch glycolate, crospovidone, using sublimation methods. Camphor was used as a sublimating agent. The prepared tablets were evaluated for thickness, uniformity of weight, content uniformity, hardness, friability, wetting time, water absorption ratio, in vitro disintegration time and in vitro drug release. The tablet disintegrate in vitro within 12-14 sec. Almost 95% of drug were released from all formulations within 10 min. The formulations containing camphor, crospovidone was found to give the best results. The tablets prepared by this method exhibited higher rate of release.

Keywords: Migraine, β-cyclodextrin, Taste masking, superdisintegrants, Mouth dissolving tablet.

INTRODUCTION

Cluster headache is a relatively rare but extremely debilitating disorder that is characterized by the rapid onset of unilateral, periorbital headache that quickly escalates to maximum intensity. Patients routinely report the pain of an attack as being the most severe they have ever experienced. By the definition of the International Headache Society, attacks typically last from 15 to 180 min when left untreated and are accompanied by one more cranial autonomic features such as ipsiletaral conjunctival injection, lacrimation and rhinorrhea or nasal congestion. In this case, a rapid onset of pharmacological effect is an often desired from drugs. This can effectively be achieved by parenteral administration, but this method may not always be convenient for the patient. Therefore, there is growing interest in developing new, non-parenteral, reliable and convenient dosage forms using administration routes where a rapidly dissolved drug is immediately absorbed into the systemic circulation Sublingual administration can offer an attractive alternative route of administration. The advantage of the sublingual drug delivery is that the drug can be directly absorbed into systemic circulation bypassing enzyme degradation in the gut and liver. In addition, the thin sublingual mucosa (about 190 µm compared to 500–800 µm of the buccal mucosa) and the abundance of blood supply at the sublingual region allow excellent drug penetration (absorption) to achieve high plasma drug concentration with a rapid onset of action. A well-established example is nitroglycerin, which is used for the treatment of acute angina. A fast dissolving system can be defined as a dosage form for oral administration, which when placed in the mouth, rapidly disperses or dissolves and can be swallowed in the form of liquid [1, 2].

Naratriptan is a triptan drug used for the treatment of migraine headaches. It is a selective 5-hydroxytryptamine1 receptor subtype agonist (5-HT1B/1D). Chemically it is N-methyl-2-[3-(1-methylpiperidin-4-yl)-1H-indol-5-yl] ethane-1-sulfonamide monohydrochloride. It is well absorbed (70% oral bioavailability), absorption is rapid with peak plasma concentrations after 2-5 hours. As migraine sufferers have markedly reduced functional ability, they would be benefited from acute treatment that helps them to resume their functional activities as quickly as possible [3].

In the present study mouth dissolving tablet of naratriptan was developed so as to achieve rapid disintegration in mouth systemic absorption and maximum peak concentration in less time. As tablet disintegrates in mouth this could enhance the clinical

effect of the drug through pre-gastric absorption from the mouth, pharynx and oesophagus this leads to an increase in bioavailability by avoiding first pass liver metabolism [4].

MATERIALS AND METHODS

Naratriptan HCl was obtained as a gift sample from Orchid Pharma Ltd. Aurangabad. Croscarmellose sodium, Sodium starch glycolate from Maple Biotech, Pune, Crospovidone from Ajanta Pharma Aurangabad., Strawberry Flavour from Cipla pharmaceuticals, Satara.

Mouth dissolving tablets of Naratriptan HCl were prepared using the superdisintegrants (Croscarmellose sodium, Crospovidone, Sodium starch glycolate) in varying concentration (1:2 and 1:3) used to develop the tablets. In this study Mouth dissolving tablets were prepared by sublimation technique six formulations of Naratriptan HCl by sublimation method using camphor as a sublimating agent [6, 7] in different proportions were prepared by using mannitol as a diluent. All the ingredients were passed through #60 mesh separately. The drug and the diluents was mixed in a small portion of both each time and blending it to get uniform mixture and set aside. The other ingredients were weighed and mixed in geometrical order, mixed thoroughly with lubricant .The tablets of weight 100mg were prepared by sublimation technique using 6.5mm punch in Karnavati tablet punching machine weighing 100mg each [8]. After that the sublimation batch were dried for 5hours for the sublimation of camphor.

The healthy human volunteers of age group 20-25 years were used for taste evaluation; informed consent was obtained from all of them. Taste evaluation was done by a panel of 10 members using time intensity method. Sample equivalent to normal dose was held in mouth for 10 sec., bitterness levels were recorded instantly and then after 10sec, 1, 2, 5, and 15 minutes and is mentioned in table. Volunteer's opinion for bitterness values were rated by giving different score values. That is, 0: no bitterness, 1: acceptable bitterness, 2: slight bitterness, 3: moderately bitterness, 4: strong bitterness [5].

Evaluation of Mouth Dissolving Tablets

Fourier Transform infrared spectroscopy

FTIR spectra were obtained on a Perkin Elmer Instruments, USA. FTIR spectrometer. Samples were prepared in KBr disks (2mg sample in 200mg KBr).The scanning range was 400-4000cm-1 and the resolution was 1cm-1.

Uniformity of Weight [9]

The weights were determined to within ±1mg by using Shimadzu Corporation, Japan. Weight control is based on a sample of 20 tablets. Determination were made in triplicate.

Tablet Hardness [10]

The crushing tolerance of tablet was measured using an Electrolab model EL500. Determinations were made in triplicate.

Tablet Friability [10]

The friability of the tablets was measured in Electrolab. Tablets of a known weight or samples of 20 tablets are dedusted in a drum for a fixed time. (100 revolution) and weight again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%. Determination was made in triplicate.

Friability = [(initial weight –final weight) / (initial weight)] x 100

Drug Content

Ten tablets were powdered and the blend equivalent to 5mg of Naratriptan HCl was weight and dissolved in suitable quantity of 0.1M HCl solution was filtered and diluted and drug content analysed spectrophotometrically at 222.20 nm using Shimadzu UV- 1800, Japan.

In-vitro Disintegration test [10]

The Test was carried out on 6 tablets using tablet disintegration tester Electrolab, Mumbai. Distilled water at 37oc ±2oc was used as a disintegration media and the time in second taken for the complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

Wetting Time [13]

The wetting time of the tablet can be measured using a simple procedure 5 circular tissue papers of 10cm diameter are placed in a Petridish with a 10cm diameter. 10ml of water. Containing amaranth a water soluble dye is added to Petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Tablet Thickness [9]

Tablet thickness can be measured using a simple procedure. Five tablets were taken and their thickness was measured using varnier Callipers. The thickness was measured by placing tablet between two arms of the varnier callipers.

Water absorption Ratio [13]

A piece of tissue paper folded twice was placed in a small Petridish containing 6ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was weighted. Water absorption ratio, R was determined using following equation.

R= Wa-Wb / Wa x 100

Where,

Wa = weight of tablet after water absorption
Wb= weight of tablet before water absorption

***In-vitro* Dissolution Study [12]**

The release rate of Naratriptan HCl from mouth dissolving tablets was determined using USP dissolution testing apparatus II (paddle method) .The dissolution test was performed using 900ml of 0.1M HCl at 37± 0.5oc and 50 rpm. A sample (1ml) of the solution was withdrawn from the dissolution apparatus at regular intervals for 15 minutes. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a membrane filter. Absorbance of this solution was measured at 222.20 nm using a Shimadzu UV- 1800, Japan double beam spectrophotometer. Cumulative percentage of drug release was calculate using an equation obtained from a standard curve.

RESULTS AND DISCUSSION

Naratriptan Hydrochloride: β cyclodextrin (1:1 to 1:10) solid dispersions were prepared by paste method to mask the bitter taste of the drug. Panel of 10 members using time intensity method were evaluated for the taste masking of drug. The ratio of drug: β cyclodextrin for taste masking was optimized to 1:8. The data in Table-1 indicates the taste evaluation of drug: β cyclodextrin (1:8) solid dispersion. The optimized drug: β cyclodextrin (1:8) solid dispersion was evaluated for drug content, bulk density, Carr's index and angle of repose as in Table-2. Drug content of drug: β cyclodextrin (1:8) was found to be 96.38 %. Drug and solid dispersion showed good flow properties.

The powder blend for all formulations containing various concentrations of Croscarmellose sodium, crospovidone, sodium starch glycolate as superdisintegrants was prepared and then the FTIR studies were done that suggests incompatibility, the study suggests that the drug and excipients are compatible to each other Fig 3 to 8. Among the soluble diluents, mannitol was selected as a diluent considering its advantages in terms of easy availability and negative heat of dissolution. Table-4 show that all the formulated tablets exhibited within the pharmacopoeial limit. From different batches. Addition of sublimating agent had no pronounce effect on hardness and increased friability of the tablets. The wetting time of the tablets were also considerably reduced in tablets. The drug content of all the formulations was found to be between 97.62 to 99.53 % which was within the acceptable limits as per USPXXVII.

The porous structure is responsible for faster water uptake, hence it facilitates wicking action of superdisintegrants in bringing about faster disintegration. Tablets with lower friability (0.48%) may not break during handling on machines. The use of sublimating agent resulted in increased friability probably due to increased porosity. Batches F1 to F6 showed good mechanical integrity, but the disintegration time was found to be less than 50sec.The results shown in Table: 05 revealed that sublimation of camphor from tablets resulted in faster disintegration the low value of wetting time and disintegration time indicates that the porosity of tablet of batch F5 would be greater than batches F1 to F6. The thickness of tablets varies from 3.00 to 3.72 mm. *In-vitro* release studies were carried out using USP tablet dissolution test apparatus paddle method at 37±0.5oc, taking 900ml of 0.1M HCl dissolution medium. Speed of rotation of the paddle was set at 50 rpm. Aliquots of 1ml were withdrawn after 2, 4, and 6, 8, 10 upto 15 min and analysed spectrophotometrically at 222.20 nm. The *in-vitro* dissolution profile fig: 02 and 03 indicate faster and maximum drug release from formulation F5. Formulation F5 prepared by sublimation method using camphor as a sublimating agent from final tablets showed release 99.85% drug at 8min.

Table-1: The Taste Evaluation of Drug: β cyclodextrin (1:8) Solid Dispersion.

Sr. No	Time (sec)	Before Taste masking	After Taste masking	
			1:10	1:8
01	10	Slight Bitter	No Bitter	No Bitter
02	60	Moderately Bitter	No Bitter	No Bitter
03	120	Moderately Bitter	No Bitter	No Bitter
04	300	Strongly Bitter	No Bitter	Acceptable Bitter
05	600	Strongly Bitter	Acceptable Bitter	Slight Bitter
06	900	Strongly Bitter	Slight Bitter	Slight Bitter

Table-2: Evaluation Of Solid Dispersion Naratriptan Hcl: Bcyclodextrin (1:8)

Parameters	Pure Drug	Solid Dispersion (1:10)	Solid Dispersion (1:8)
Drug Content (%)	100	94.27±2.0	96.38±0.57
Bulk Density	0.58±0.01	0.62±0.01	0.60±0.01
Carr's Index	12.61±1.0	14.36±0.80	17.93±0.58
Angle of Repose	26.24±1.09	31.58±0.30	30.57±0.73

Table-3: Formulation Composition for Tablets Prepared By Using Superdisintegrants

Ingredients	Formulations(all quantities in milligrams)					
	F1	F2	F3	F4	F5	F6
Naratriptan HCl	2.5	2.5	2.5	2.5	2.5	2.5
β-Cyclodextrin	25	25	25	25	25	25
Croscarmellose sodium	5	-	-	7.5	-	-
Crospovidone	-	5	-	-	7.5	-
Sodium starch glycolate	-	-	5	-	-	7.5
Mannitol	33.33	33.33	33.33	33.33	33.33	33.33
Microcrystalline cellulose	15.17	15.17	15.17	12.67	12.67	12.67
Camphor	15	15	15	15	15	15
Strawberry flavour	2	2	2	2	2	2
Sodium saccharine	1	1	1	1	1	1
Magnesium Stearate	1	1	1	1	1	1
Total	100	100	100	100	100	100

Table-4: Pre-Compression Parameters of Tablets Prepared By Sublimation Technique

Parameter	Formulations Code					
	F1	F2	F3	F4	F5	F6
Bulk density (gm/ml)	**0.500**	**0.476**	**0.434**	**0.588**	**0.555**	**0.625**
Tapped density (gm/ml)	**0.588**	**0.555**	**0.500**	**0.666**	**0.625**	**0.714**
Angle of repose (^{O})	**29.14**	**27.50**	**25.11**	**24.44**	**23.31**	**22.83**
Carr's index (%)	**14.96**	**14.23**	**13.2**	**11.81**	**11.2**	**12.46**
Hausner's ratio	**1.17**	**1.16**	**1.15**	**1.13**	**1.12**	**1.14**

Table-5: Evaluation of Mouth Dissolving Tablets.

Formulations	F1	F2	F3	F4	F5	F6
Weight Variation	99.88	99.23	101.23	98.96	99.36	99.67
Hardness (Kg/cm^2)	3.1±0.15	3.0±0.10	3.3±0.10	2.9±0.10	3.1±0.11	3.2±0.20
Friability	0.72±0.02	0.49±0.011	0.60±0.01	0.64±0.04	0.63±0.04	0.53±0.03
Drug content (%)	98.96	97.90	97.62	98.69	99.53	98.59
Thickness (mm)	3.5±0.05	3.6±0.17	3.7±0.10	3.0±0.11	3.1±0.25	3.2±0.20
Disintegration Time (sec)	47	19	34	44	14	25
Wetting time (Sec)	21±1.0	14±0.57	18±2.0	19±0.57	12±2.0	18±1.73
Water absorption ratio	55.0±1.15	69.12±0.57	60.12±1.0	60.53±1.5	79.06±1.0	67.36±2.5

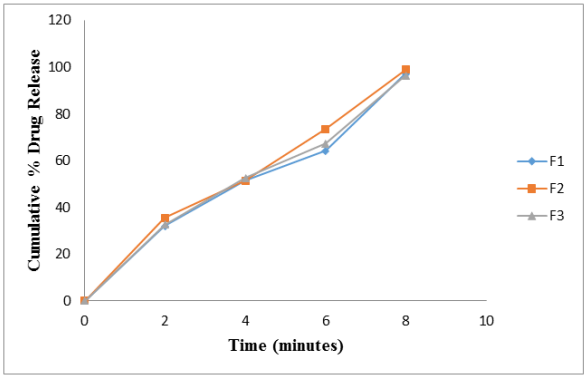

Fig-1: *In-vitro* Dissolution curve of F1, F2, F3 between Cumulative Percent Release against Time

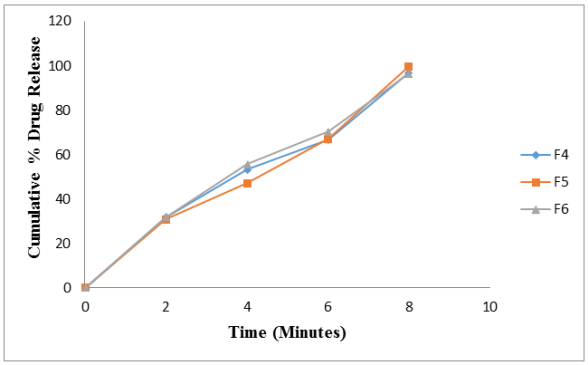

Fig-2: *In-vitro* Dissolution curve of F4, F5, F6 between Cumulative Percent Release against Time

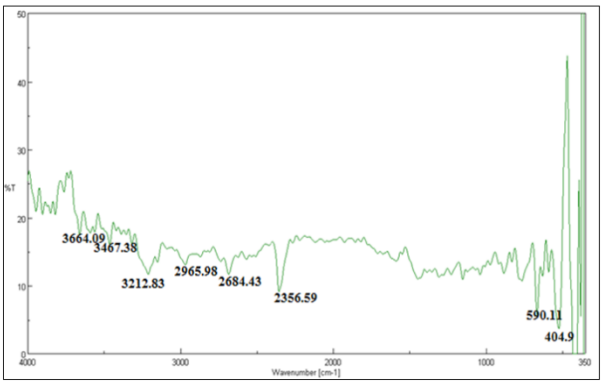

Fig-3: FT-IR spectrum of Naratriptan hydrochloride

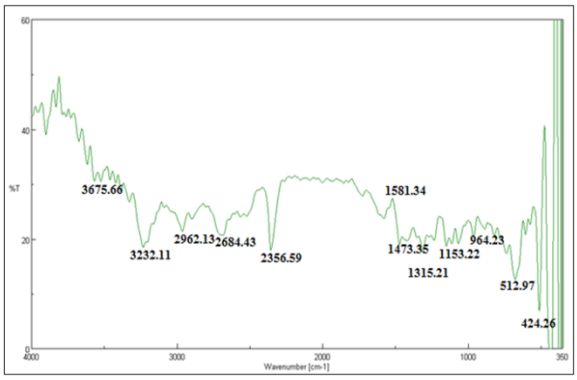

Fig-6: FT-IR Spectrum of Naratriptan HCl and CCS mixture

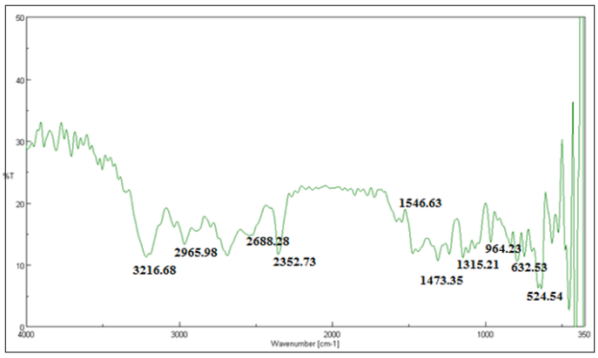

Fig-4: FT-IR Spectrum of Naratriptan HCl and Crosspovidone mixture

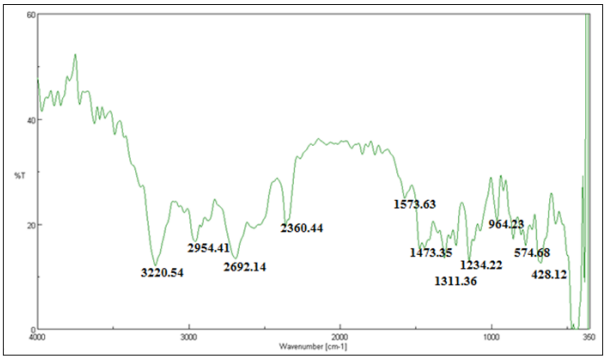

Fig-7: FT-IR Spectrum of Naratriptan HCl and Camphor mixture

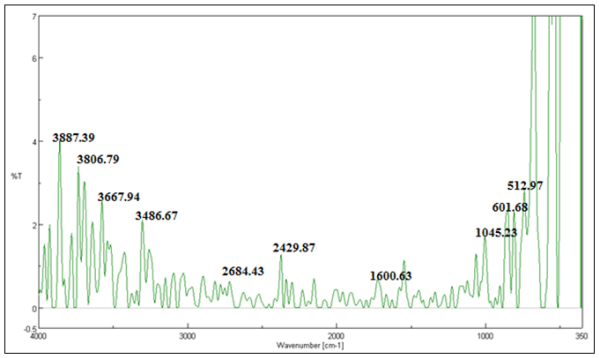

Fig-5: FT-IR Spectrum of Naratriptan HCl and Sodium starch glycolate mixture

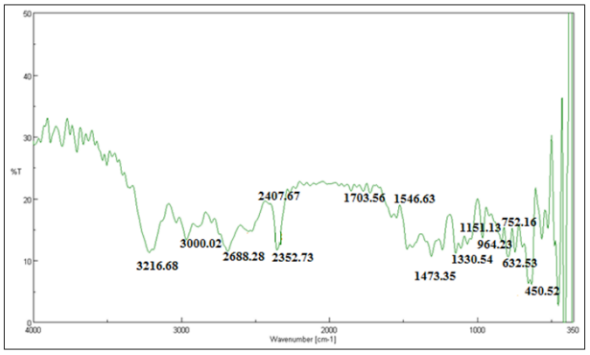

Fig-8: FT-IR Spectrum of Naratriptan HCl and β-cyclo dextrin

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