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RESEARCH ARTICLE

Formulation and Evaluation of Naratriptan Orodispersible Tablets Using Superdisintergrants by Direct Compression Method

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ABSTRACT

The present study deals with the formulation and evaluation of Orodispersible tablets (ODT) of Naratriptan, a typical Antimigraine drug which is highly appropriate as it has ease of administration for mentally ill, disabled and uncooperative patients. ODTs have better patient acceptance, compliance, improved biopharmaceutical properties and efficacy compared with conventional oral dosage forms as they quickly disintegrate/dissolve/disperse in saliva. In the present research work, an attempt was made to design ODTs by addition of super disintegrants. Experimental design was run with four batches containing different concentration of super disintegrants. The optimization results revealed that the effect of super disintegrants result in good disintegration profile of 7-8sec (Ideal ODT should disintegrate within 1min), dissolution profile shows that more than 90% of the drug releases within 10 minutes, and good dispersion pattern. Crospovidone (5%) and Croscarmellose sodium (4%) are better super disintegrants. The formula F4 possesses good disintegration and dissolution profile with additions of super disintegrants. The prepared tablets by direct compression using super disintegrants pass all the quality control tests and FTIR studies reveal that there is no interaction between drug and excipients. This method can also be used to prepare ODTs of antiemetics, antiallergics, and cardiovascular agents etc which needs rapid onset of action. Thus, faster disintegration and dissolution of Naratriptan ODT may give better therapy for the treatments of Migraine.

KEYWORDS

Orodispersible tablets, Naratriptan, FTIR, L1% values

INTRODUCTION

The US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, an ODT as “a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue”[8]

The concept of oral drug delivery system emerged from the desire to provide patients with conventional means of talking their medication. Difficulty in swallowing.

The significance of these dosage forms is highlighted by the adoption of the term, “Orodispersible Tablet”, by the European Pharmacopoeia (5.0, 2005) adopted the term "orodispersible tablet" as a tablet to be placed in the mouth where it disappears rapidly before swallowing,[1]

Orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts.[2]

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Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient's compliance. Orally disintegrating tablets offer an advantage for population who has difficulty in swallowing. It has been reported that Dysphasia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting and motion sickness complications.[2]

To overcome this weakness, scientists have developed innovative drug delivery system know as orally disintegrating tablets (ODTs). These are novel types of tablets disintegrates/dissolve/disperse in saliva. Their characteristic advantages such as administrating without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden, and patients who do not have easy access to water. The benefits, in terms of patient's compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market.[3, 20]

Recent advances in novel drug delivery system (NDDS) aim to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance.[9]

MATERIALS AND METHODS

Naratriptan was obtained as gift sample from orchid Indian ltd, Croscarmellose sodium, Crospovidone, Microcrystalline cellulose were obtained from SD fine chemical Ltd, Mumbai.

Preformulations

Identification of the drug was carried out by FTIR (Shimadzu 8101A, Mumbai). Standardization of the drug was carried out using UV/Vis spectrophotometer (Perkin Elmer, Mumbai). FTIR spectral analysis of the formulations was performed to assess drug excipient compatibility. Preliminary studies were carried out on the tablets using different concentrations of superdisintegrants. Thus, after evaluation of the quality parameters and subjecting to *in vitro* disintegration and *in vitro* dissolution studies the final concentrations of the superdisintegrants were optimized. Based on this preformulation data the optimized formulations for further investigations were decided.

Preparation of Tablets

Accurately weigh Naratriptan, fillers, super disintegrants, sweetener and flavor. Mix Naratriptan part quantity of filler and co-sift through ASTM #60. Sift remaining quantity of filler, super disintegrants, sweetener and flavors through ASTM#40. Blend the sifted material together for 5 minutes. Weigh and sift magnesium stearate through ASTM # 40. Lubricate the blend with sifted magnesium stearate for 2 min. Compress the above blend in CEMACH Mini Rotary Tableting Machine using 8mm concave punches, upper punch embossed with 'c'.

Table 1: Formulation Design: Selection of diluents

Sr N	Ingredient	F1	F2	F3
1	Naratriptan	1.11	1.11	1.11
2	Mannitol	--	83.4	--
3	Lactose Monohydrate	83.4	--	--
4	Avicel ph 101	--	--	83.5
5	Ac-Di-Sol	4	4	4
6	Kollidon	5	5	5
7	Aspartame	3	3	3
8	Orange flavor	2	2	2
9	Magnesium stearate	1.5	1.5	1.5
10	Average weight	100	100	100

Table 2: Optimization of super disintegrants

Sr No	Ingredient	F4	F5	F6	F7	F8
1	Naratriptan	1.11	1.11	1.11	1.11	1.11
2	Mannitol	50.00	50.00	50.00	55.00	54.00
3	Lactose Monohydrate	33.39	38.39	37.39	--	--
4	Avicel ph 101	--	--	--	33.39	33.39
5	Ac-Di-Sol	4	4	--	4	--
6	Kollidon	5	--	5	--	5
7	Aspartame	3	3	3	3	3
8	Orange Flavor	2	2	2	2	2
9	Magnesium Stearate	1.5	1.5	1.5	1.5	.1.5
10	Average weight	100	100	100	100	100

Table 3: Optimization of lubricant

Sr N	Ingredient	F9	F10	F11
1	Naratriptan	1.11	1.11	1.11
2	Mannitol	50.0	50.5	49.5
3	Lactose Monohydrate	--	33.39	33.39
4	Avicel Ph 101	33.39	--	--
5	Ac-Di-Sol	4	4	4
6	Kollidon	5	5	5
7	Aspartame	3	3	3
8	Orange flavor	2	2	2
9	Magnesium stearate	1.5	1	2
10	Average weight	100	100	100

Evaluation of Tablets

The formulations were evaluated for hardness, weight variation, thickness, friability, disintegration time, *in vitro* dispersion time, wetting time and water absorption ratio, assay, content uniformity and *in vitro* dissolution.

***Hardness Test*[10, 13]**

Tablets require a certain amount of strength or hardness and resistance to friability to withstand mechanical shock of handling in manufacture, packing and shipping. To perform this test tablets were placed between two anvils, force to the anvils and the crushing strength that just causes the tablets to break was recorded. Monsanto hardness tester was used to measure the hardness of tablets. Six tablets from each batch were used for hardness studies and results were expressed in kg/cm^2.

***Weight Variation Test*[10, 17]**

Randomly, twenty tablets are selected during compression and the mean weight was determined none of the tablets should deviated from the average weight by more than ±7.5%.

***Thickness*[9]**

The thickness of the tablet was measured using vernier Caliper. It is expressed in mm.

***Friability*[2, 12, 13]**

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm/min for 4min dropping the tablets at distance of 6 inches with each revolution. Preweighed sample of 20

tablets were placed in the friabilator. Tablets were dedusted and reweighed.

The percent friability was measured using the formula:

Friability = Initial weight-Final weight/Initial weight x100

Disintegration Time[9]

The *in vitro* disintegration time was determined using disintegration test apparatus. Six tablets were placed in each of the six tubes of the apparatus. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

In-vitro Dispersion Time[9,16,19]

In vitro dispersion time was measured by dropping a tablet in measuring cylinder containing 6 ml of water Three tablets from each formulation were randomly selected and *In vitro* dispersion time was performed.

Wetting Time Water Absorption Test [11, 16, 18]

Wetting time is closely related to the inner structure of tablets and to the hydrophilicity of the excipients. According to the following equation proposed by Washburn E. W., the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders.

$$dl/dt = r\gamma\cos\theta / (4\eta l)$$

Where, l = length of penetration,

r = capillary radius,

γ = surface tension,

η = liquid viscosity,

t = time

θ = contact angle.

It is obvious that pore size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting time is an important step for disintegration process to take place.

A piece of tissue paper folded twice was placed in a small petridish (internal diameter = 6.5 cm) containing 6 ml of water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37^0C.

The same procedure was repeated for determining water absorption ratio. The wetted tablet was then weighed. Water absorption ratio, R, was determined according to following equation:

$$R = \{(W_a - W_b)/ W_a\} X100$$

Where, W_a = Weight of tablet before study.

W_b = Weight of tablet after study.

R = water absorption ratio.

Assay[9]

20 tablets were weighed and triturated. The tablet triturate equivalent to 1.11mg of the drug was weighed accurately dissolved in 0.1 N HCL and diluted to 100ml with 0.1 N HCL and assayed individually at respective λ max against the reagent blank. The drug content should be within 90% to 110% of the labeled claim.

Uniformity of dosage units[10]

Uniformity of dosage units is defined as the degree of uniformity in the amount of drug substance in each unit.

As per (USP 30 NF 25) uniformity of dose units was performed.

Table for Application of content uniformity (CU) and weight variation test (WV) for tablet dosage form USP was presented below.

Uniformity of dosage units performed by content uniformity method because percentage of drug is less than 25mg.

Content Uniformity[10]

10 dosage units are assayed individually and the acceptance value is calculated.

Table 4: (USP 30 NF 25)

			Dose and ratio of drug substance ≥25mg&≥ 25%	Dose and ratio of drug substance <25mg&< 25%
Tablets	Uncoated	--	WV	CU
	Coated	Film Coated	WV	CU
		Others	CU	CU

Acceptance Value = $\left| M - \bar{X} \right| + ks$

Where, M - Reference Value

$\bar{X}$ - Mean of individual contents

k - Acceptability Constant [If n = 10 then k = 2.4 and if n = 30 then k = 2.]

s - Sample Standard deviation

Calculation of L1% Value

Acceptance Value = $\left| M - \bar{X} \right| + ks$

Where, $\bar{X}$ = 102.7

If $\bar{X}$ >101.5% then M = 101.5

If n = 10 then k = 2.4, if n = 30 then k = 2

S = standard deviation

AV = $\left| M - \bar{X} \right| + ks$

AV = $\left| 101.5-102.7 \right| +2.4\times5.3$

AV = 1.2+12.72

AV = 13.39

Maximum allowed acceptance value is 15 unless otherwise specified

In vitro Dissolution Studies[12]

The *in vitro* dissolution study was carried out in USP dissolution test apparatus Type II (paddle). Samples were withdrawn at 5, 10, and 15 minutes time intervals by replacing with same dissolution medium and the dissolution of the drug was expressed as percentage drug dissolved by using following formula.

Dissolution Parameters[10]

As per USP (USP 30 NF25) the recommended dissolution medium for Naratriptan is 0.1 N HCL. Hence 0.1 N HCL was selected as a medium.

Preparation of Medium (0.1N HCl pH 1.2

8.5 ml of hydrochloric acid was diluted with distilled water and volume made upto 1000ml

Dissolution Medium : 0.1N HCl, 500 ml

RPM : 50

Apparatus : USP Type II (Paddle)

Temperature : 37 ± 0.5 °C

Withdrawal time points: 5, 10, 15 min

Volume withdrawn : 5 ml

RESULTS AND DISCUSSION

Infrared Spectroscopic Study

Naratriptan hydrochloride, excipients and their combination were analyzed by Infrared spectroscopy (FTIR 8400S) by KBr pellet method. They are compressed under high pressure in a hydraulic press to form a transparent pellet. The pellet was scanned from 4000 to 400-cm^{-1} 1n FTIR. The changes in the obtained peaks of pure drug excipients were compared with the drug- excipients mixture.

Table 5: Characteristics peaks

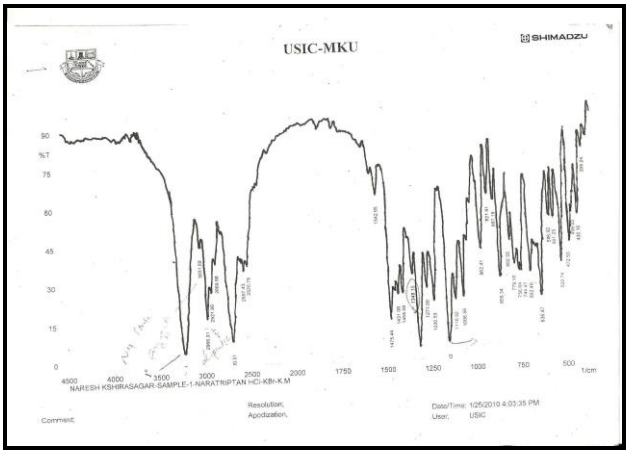

Figure 1: FTIR of Naratriptan pure drug

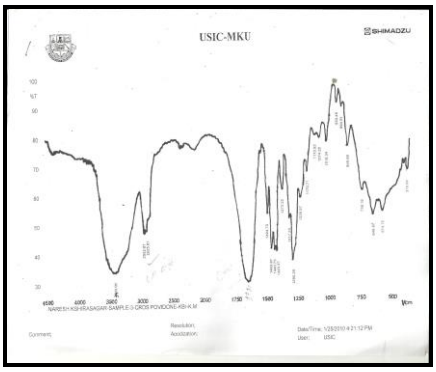

Figure 2: FTIR of Kollidon

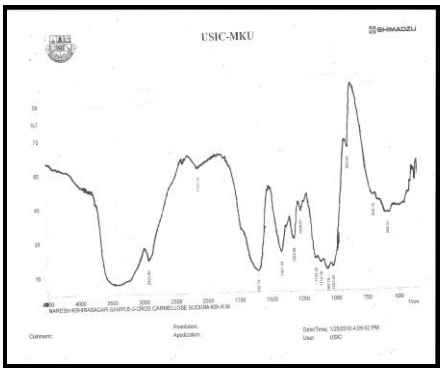

Figure 3: FTIR of Ac-Di-Sol

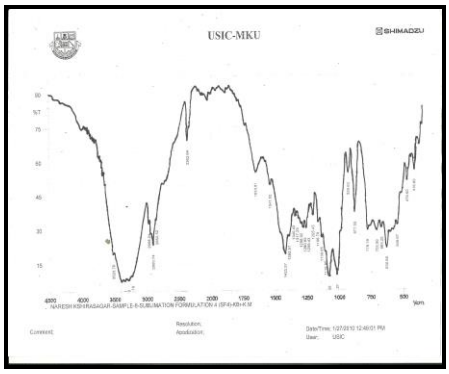

Figure 4: Formulation F4

Table 5: Characteristics peaks

	Naratriptan	Crospovidone	Croscarmellose	F4
(Frequency Cm^{-1})	3031.89			3031.89
		2952.81		2952.81
	2966.31			2966.31
		1732.00		1732.00
	1348.15			1348.15
		3500.00		3500.00
	3395.00			3395.00
			2921.96	2921.96
			3500.00	3500.00
			1602.74	1602.74

Table 6: Evaluation of Tablets F1-F3

Sr N	Evaluation	F1	F2	F3
1	Weight variation (mg)	101.2 ± 0.4	102.1±0.3	100.1±0.3
2	Thickness (mm)	2.34-2.36	2.49-2.50	2.41-2.43
3	Friability (%)	0.31	--	0.41
4	Hardness (kg/cm^2)	1.5-2	1-1.5	2-3
5	Disintegration time (s)	8-10	10-12	14-15
6	Dispersion time (s)	8-10	10-11	9-10
7	Content uniformity (L_1)	1.72	1.01	1.21
8	Water absorption ratio	62-64	65-67	65-66
9	Assay (%w/w)	100.8	100.3	99.8
10	Wetting time (s)	18-20	18-19	19-21

Table 7: Evaluation of Tablets F4-F8

Sr N	Evaluation	F4	F5	F6	F7	F8
1	Weight variation (mg)	103.3±0.2	103.2±0.1	102.3±0.3	103.2±0.2	103.1±0.2
2	Thickness (mm)	2.39-2.41	2.36-2.38	2.33-2.35	2.37-2.39	2.41-2.42
3	Friability (%)	0.39	0.46	0.47	0.48	0.43
4	Hardness (kg/cm^2)	1.5-2.5	1.5-2.5	1.5-2.5	1.5-2.5	1.5-2.5
5	Disintegration time (s)	7-8	8-10	8-10	5-7	7-8
6	Dispersion time (s)	6-8	8-10	8-10	8-10	9-10
7	Content uniformity (L_1)	1.01	1.21	0.95	1.15	1.19
8	Water absorption ratio	64-66	64-66	65-67	63-65	64-66
9	Assay (%w/w)	99.8	104.4	99.8	100.8	100.6
10	Wetting time (s)	19-20	20-21	19-20	19-20	19-20

Table 8: Evaluation of Tablets F9-F11

Sr N	Evaluation	F9	F10	F11
1	Weight variation (mg)	101.5±0.3	101.5±0.1	102.5±0.3
2	Thickness (mm)	2.37-2.39	2.36-2.39	2.38-2.39
3	Friability (%)	0.47	0.41	0.49
4	Hardness (kg/cm^2)	1.5-3	1.5-2	1.5-2
5	Disintegration time (s)	10-11	8-10	8-10
6	Dispersion time (s)	8-10	9-10	9-11
7	Content uniformity (L_1)	0.95	0.54	0.77
8	Water absorption ratio	65-66	64-65	64-65
9	Assay (%w/w)	99.6	100.6	100.8
10	Wetting time (s)	19-20	20-22	20-21

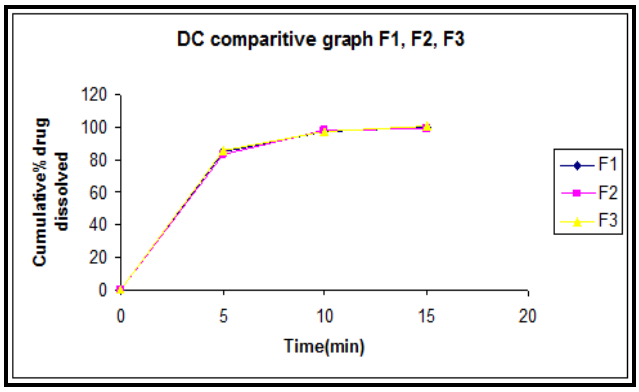

Figure 6: Comparative study on dissolution profile of DC batch F1-F3.

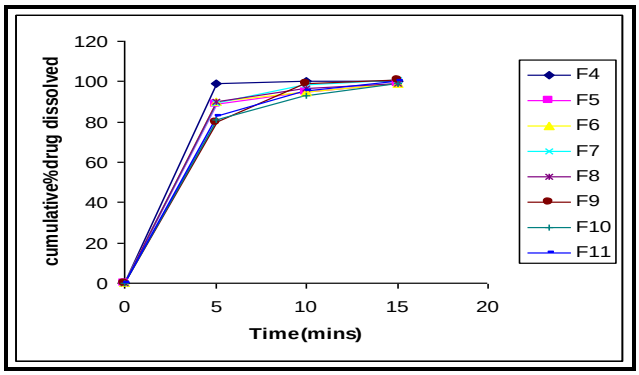

Figure 7: Comparative study on dissolution profile of DC batch F4-F11

Orodispersible tablets (ODT) of Naratriptan a typical Antimigraine drug is highly appropriate as it has ease of administration for patients who are mentally ill, disabled and uncooperative,

ODT have better patient acceptance and compliance, may offer improved biopharmaceutical properties and improved efficacy compared with conventional oral dosage forms as the drug dissolves in saliva, it bypasses enterohepatic circulation and prevents first-pass metabolism if it is absorbed in mouth.

In the present research work an attempt was made to design ODT by using addition of super disintegrants method. In this addition method the effect of dilution, their combination and effect of super disintegrants were resulted, followed by effect of lubricants were resulted.

The optimization results revealed that the effect of super disintegrating agents results in good disintegration profile, dissolution profile, and dispersion pattern. From the results obtained the following points can be summarized.

The ODTs were prepared and the disintegration time was found 7-8 sec in Formulation F4 which is in the acceptable limit as ideal ODT should disintegrate within a min. The ODT of selected drug candidates passes the all quality control tests. It can be concluded that Crospovidone (5%) and Croscarmellose sodium (4%) are better super disintegrants for formulation of Orodispersible tablets of Naratriptan.

In the finalized batches by addition of super disintegrants (F4) dissolution results shows more than 90%of the drug release within 10 minutes, which is significant in the bioavailability of water soluble drugs. It is confirming that the addition of super disintegrants method is suitable for the preparation of Naratriptan ODT.

CONCLUSION

From the results of the study, we conclude that formula F4 (Mannitol, lactose monohydrate, Croscarmellose sodium, Crospovidone, Magnesium stearate, Aspartame, orange flavor.) pocesses good disintegration and dissolution profile with additions of super disintegrants (Crospovidone Croscarmellose sodium). On comparing with their respective batches the prepared tablets by DC they passing all the quality control test viz., friability, disintegration time dispersion time, wetting time. FTIR studies reveal that there is no interaction between drug and excipients. The addition of super disintegrants method can be used to prepare ODTs of several categories of drug such as anti-emetics, antiallergics cardiovascular agent's analgesic neuroleptics which need rapid onset of action. Faster disintegration of orally disintegrating tablets of above mentioned pharmacological categories improves the availability of drug for absorption in a faster rate. This may enhance the bioavailability. Faster disintegration and dissolution of Naratriptan ODT may give better therapy for the treatment of Migraine.

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